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(*R*)- AND (*S*)-2,3-O-ISOPROPYLIDENEGLYCERALDEHYDE IN STEREOSELECTIVE ORGANIC SYNTHESIS

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CONTENTS

1. INTRODUCTION

Contemporary asymmetric synthesis is a widely used method for stereocontrolled creation of C—C bonds in organic molecules.[1] During recent years, this approach to organic synthesis greatly contributed to progress in the directed introduction of various functionalities, and in the highly controlled formation of new centres of chirality. These processes still remain the basic problems in the total synthesis of natural products. Preparation of the latter in optically pure form by application of chiral starting materials is very advantageous, enabling precise planning and efficient realization of synthetic pathways. Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules.[2] 2,3-O-Isopropylideneglyceraldehyde (**1**) is one of the chosen compounds; it is characterized by ready availability of both enantiomers from natural sources, and by pronounced versatility due to the presence of the aldehyde and protected diol functionality in the molecule (Fig. 1).

On account of the increasing interest of chemists in **1**, reflected by the augmenting number of relevant publications, and in view of our belief that its further potential applications may be very important, we resolved to gather and present the actual knowledge concerning the use of **1** in stereocontrolled organic synthesis. In the present review we shall focus attention mainly on the reactions using the carbonyl group of **1** to form a new centre of chirality (nucleophilic additions, aldol condensations and cycloadditions). The main part of the review is preceded by a presentation of methods for the preparation of both enantiomers of **1** and of its analogues containing other protective groups of the diol functionality, as well as by discussion of simple transformations of (*R*)- and (*S*)-**1** into

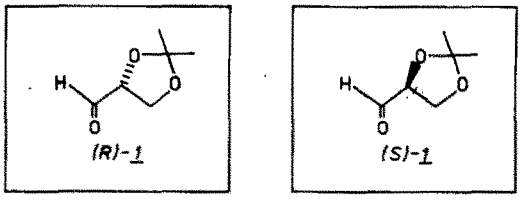


Fig. 1.

other useful chiral C_3-synthons. Wittig reactions and stereocontrolled functionalization of the resulting double bond are also surveyed. Finally, some selected examples of total syntheses of natural products using 1 as a starting material are given.

2. PREPARATION OF (*R*)- AND (*S*)-2,3-O-ISOPROPYLIDENEGLYCERALDEHYDE (1)

The first effective preparation of (*R*)-2,3-O-isopropylideneglyceraldehyde (1) was reported by Baer and Fischer in 1939.[3] D-Mannitol (2), a naturally occurring inexpensive polyhydroxy compound, was used as a starting material. Bis(acetonide) of D-mannitol (3) was prepared in 55% yield, and the resulting diol was cleaved with lead tetraacetate to give (*R*)-1 in 76% yield[4] (Scheme 1).

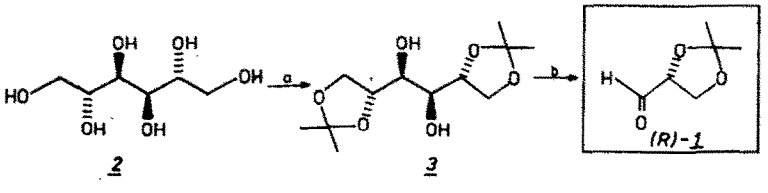
In recent years, several modifications of this classical, but still most often applied method were reported. As concerns the first stage of preparation of compound 3 from 2, modifications of Chittenden,[5] Debost *et al.*[6] and Kierstead *et al.*[7] are noteworthy. The former modification involves the use of 2,2-dimethoxypropane (instead of acetone) in 1,2-dimethoxyethane, in the presence of tin(II) chloride.[5] The second one concerns the use of 2-methoxypropane in anhydrous dimethylformamide, in the presence of catalytic amounts of *p*-toluenesulfonic acid.[6] The latter modification consists of the action of 2,2-dimethoxypropane on D-mannitol (2) in the presence of *p*-toluenesulfonic acid in dry dimethylsulfoxide as a solvent; this procedure not only affords a higher yield (62%), but also enables a reduction of the volume of solvents and greatly simplifies the work-up.[7] Recently, Kuszmann *et al.*[8] studied in detail and compared, using gas–liquid chromatographic techniques, three methods of preparation of 3: the classical one,[3,4] later improved by Tipson and Cohen[9] and those proposed by Chittenden[5] and Debost *et al.*[6] In each reaction isomeric diacetals were formed, but the method of Baer and Fischer[3,4] gave 1,2:5,6-diacetal 3 in the highest yield (63%).[8]

As concerns modifications of the second stage dealing with cleavage of the vic-diol grouping in 3, they involve replacement of lead tetraacetate by sodium periodate[10–12] or by catalytic amounts of bismuth derivatives: μ-oxo-bis(chlorotriphenylbismuth)[13] or triphenylbismuth,[14] as well as the substituted guanidinium salt of *m*-iodoxybenzoic acid.[15]

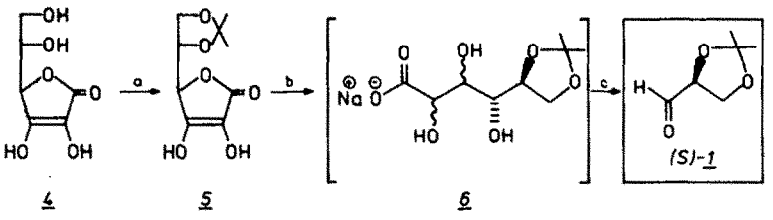
In contrast to (*R*)-2,3-O-isopropylideneglyceraldehyde (1), enantiomer (*S*)-1 is not readily available. Among a few of the so far published methods for the preparation of (*S*)-1, the first one involved a reaction sequence (analogous to Scheme 1) starting from unnatural L-mannitol which must be made from L-mannose[16,17] (and ultimately from L-arabinose[16] or L-inositol).[18]

Another convenient method for (*S*)-1 preparation, consisting in degradation of ascorbic acid (4), was proposed by Jung and Shaw[19] (Scheme 2).

The saturated diol function of ascorbic acid (4) could be easily and cleanly protected as acetonide 5; among the many procedures applied, the simplest one was to dissolve 4 in an excess of acetone containing a catalytic amount of acetyl chloride.[20] The subsequent multistep one-pot procedure of the preparation of (*S*)-1 from 5 proved to be very successful.[19] Treatment of 5 with one equivalent of sodium



Scheme 1. Reagents: (a) Me_2CO, $ZnCl_2$; (b) $Pb(OAc)_4$, benzene or EtOAc.

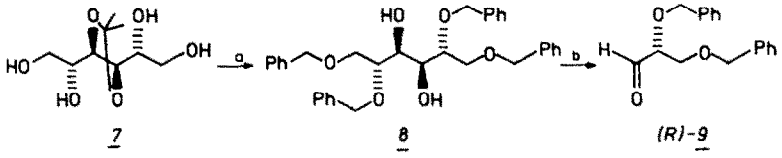


Scheme 2. Reagents: (a) Me_2CO, AcCl; (b) (i) $NaBH_4$, (ii) NaOH, (iii) H^+, pH 7; (c) $Pb(OAc)_4$, EtOAc.

borohydride presumably reduces the ene-diol functionality. Cleavage of borate esters and lactone with excess sodium hydroxide, followed by careful neutralization, probably produces acetonide carboxylate **6**, although the latter could not be isolated from the inorganic materials, and all attempts to form the corresponding free acid also led to hydrolysis of the ketal. The dry mixture of salts containing **6** was treated with 3.5 equivalents of lead tetraacetate in ethyl acetate to cleave all vic–glycol bonds and to produce (*S*)-**1** in solution. This method was simplified and adapted to the large scale by Takano *et al.*[21]

Other, less efficient methods for preparation of (*S*)-**1** from inexpensive, naturally occurring materials (e.g. D-sorbitol) were also investigated.[22]

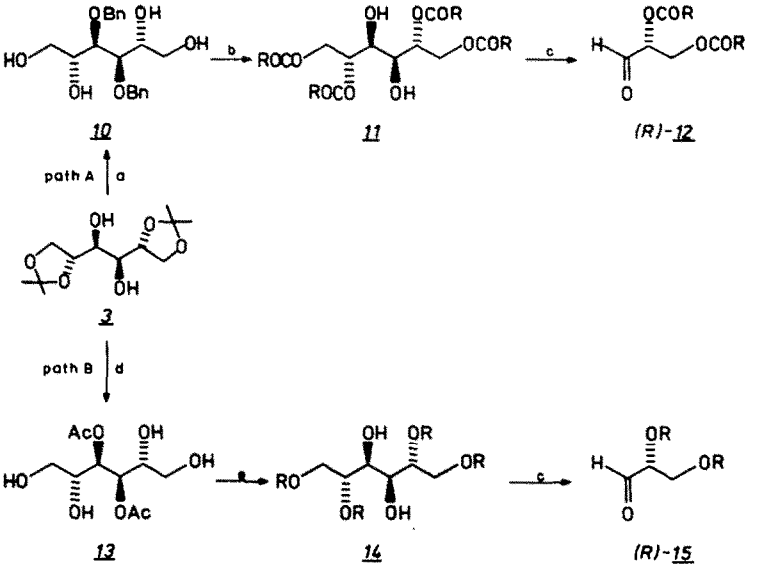
Whereas 2,3-O-isopropylideneglyceraldehyde (**1**) is most widely used, there are reports on applications of other groups protecting the diol function: O-dimethyl,[23] O-dibenzyl,[24–26] O-carbonate,[27] O-dibenzoyl[28] and O-cyclohexylidene.[29] Preparation of (*R*)-2,3-di-O-benzylglyceraldehyde (**9**) is presented in Scheme 3.



Scheme 3. Reagents: (a) (i) $PhCH_2Cl$, NaH, (ii) H^+, H_2O; (b) $Pb(OAc)_4$, EtOAc.

3,4-O-Isopropylidene derivative **7**, readily available from D-mannitol, was benzylated under standard conditions and hydrolyzed to **8**, whereupon it was cleaved with lead tetraacetate to compound **9** in 50% yield.[25]

Recently, a general approach to the synthesis of O-acylated (Scheme 4, path A) as well as acetal or O-silylated (path B) derivatives of glyceraldehyde was developed.[30]



Scheme 4. Reagents: (a) (i) $PhCH_2Br$, $n\text{-}Bu_4N^+Br^-$, (ii) H^+, H_2O; (b) (i) RCOCl, pyridine, (ii) H_2, Pd/C; (c) $Pb(OAc)_4$, benzene; (d) (i) Ac_2O, Et_3N, (ii) H_2O; (e) (i) acetalization or silylation conditions, (ii) $LiAlH_4$, THF.

The bis(acetonide) of D-mannitol (3) was benzylated (path A) or acetylated (path B), whereupon both the benzyl and acetyl derivative, were hydrolyzed to give 10 and 13, respectively, 10 treated with an acylation agent and then catalytically hydrogenated afforded derivative 11 which was cleaved with lead tetraacetate to produce protected glyceraldehyde (*R*)-12. In this manner, (*R*)-2,3-di-O-acetyl-, -benzyl-, and -carbonateglyceraldehyde were obtained in satisfactory yields.[30]

3,4-Di-O-acetyl-D-mannitol (13) treated with an appropriate carbonyl compound or silyl chloride under acetalization or silylation conditions afforded the corresponding derivative of D-mannitol which was reduced with lithium aluminium hydride to give 14. The vic-diol grouping of 14 was cleaved under standard conditions to produce glyceraldehyde derivative (*R*)-15. In this manner (*R*)-2,3-O-cyclohexylidene- and -di-O-t-butyldimethylsilylglyceraldehyde were obtained in good yields.[30]

2,3-O-Isopropylideneglyceraldehyde (1) can be readily and efficiently obtained even on large preparative scale, but its stability is limited owing to the tendency to polymerization, thus it should be used immediately after preparation. However, when desirable it can be stored as frozen benzene solution; in this case, distillation before use is recommended.[31]

3. SIMPLE TRANSFORMATIONS OF (*R*)- AND (*S*)-1-CHIRAL C_3-SYNTHONS

2,3-O-Isopropylideneglyceraldehyde (1) is an important starting compound for the preparation of many C_3-synthons which are widely applied in organic synthesis as chiral building blocks. This section presents the methods for obtaining the most frequently used chiral C_3-synthons and also shows examples of their application in the synthesis of various important organic compounds. Other ways of utilization of these chiral intermediates are listed in the Section 7.

The key C_3-synthons obtained from (*R*)-1, which in turn can be used as starting compounds for preparation of other chiral building blocks, are shown in Fig. 2. Obviously, these compounds can be synthesized in the form of their mirror images, when starting from enantiomer (*S*)-1.

Compound (*R*)-1 was usually reduced to (*S*)-2,3-O-isopropylideneglycerol (16) with hydrogen, in the presence of a nickel catalyst.[32] However, in recent years sodium borohydride was widely used for reduction of (*R*)-1[33] and (*S*)-1.[19] Compound (*R*)-16 can be obtained not only from (*S*)-1 or from its precursors, but also from other natural sources, e.g. L-serine.[34] Enantiomers of glycerol acetonide (16) serve as key intermediates in the synthesis of an array of chiral building blocks, as shown in Fig. 2. Tosylate (*R*)-17 can be obtained by the procedure of Sowden and Fischer[35] (*p*-toluenesulfochloride in pyridine), with modifications proposed by other authors.[19,33,36,37] When starting from (*R*)-17, one can prepare both enantiomers of propylene epichlorohydrin (18), also being an important C_3-synthon (Scheme 5).

The synthetic scheme is relatively straightforward, however, several points require some comments. The reaction of 22 with one equivalent of triphenylphosphine in carbon tetrachloride–dimethylformamide gave a mixture containing 23 and triphenylphosphine oxide. The final step in the synthesis of (*S*)-18 required selective reversion of the ends of the three-carbon unit. This could be accomplished by first preparing (*R*)-glycidol 24 which was then used for the synthesis of 25.[38]

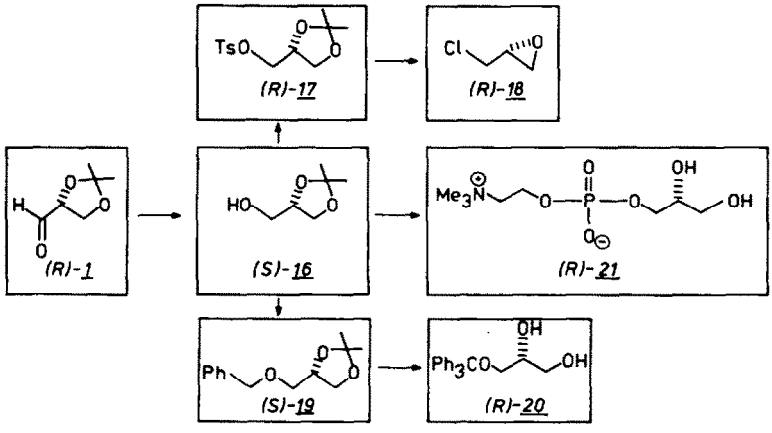
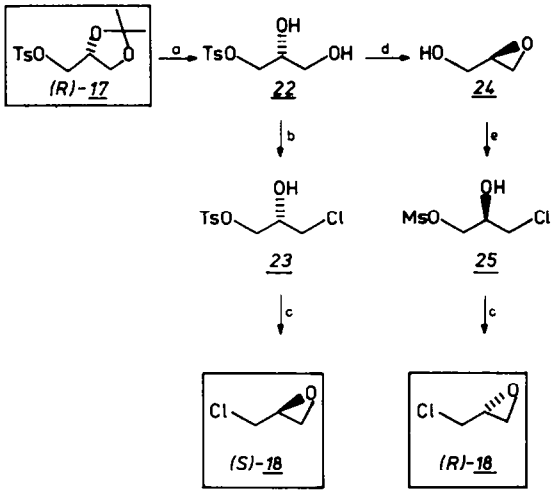


Fig. 2.



Scheme 5. Reagents: (a) 1 N HCl, Me_2CO; (b) PPh_3, CCl_4, DMF; (c) Na, $(CH_2OH)_2$; (d) MeONa, MeOH; (e) (i) MsCl, Et_3N, (ii) $HCl_{conc.}$

Compound (*R*)-**18** could be readily obtained from **25** by treatment with base. The remaining propylene epihalogenohydrins can be obtained by the recently reported method of Kawakami *et al.*[39] (Scheme 6).

1-O-Benzyl derivative of (*S*)-2,3-O-isopropylideneglycerol (**19**) is the next important chiral C_3-synthon (Fig. 2); it could be obtained in good yield by the procedure of Baer and Buchnea[11,37,40] (benzyl bromide, sodium hydroxide), modified by using phase-transfer catalysts.[41,42] In turn, the benzyl derivative (*S*)-**19** could be converted into the analogue of trityl derivative **20**,[43] which is very useful in the synthesis of unsaturated lipids (Scheme 7).

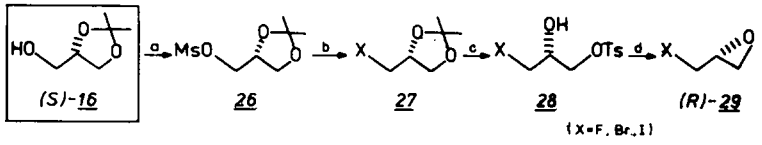
The above present reaction scheme calls for some comments. After hydrolysis, (*S*)-**19** was protected by introduction of the carbonate function, thus affording **31**. The subsequent reaction steps: deprotection of the benzyl function, tritylation and removal of carbonate protection yielded the desired (*R*)-**33**. The latter—with opposite configuration- was obtained by another path, with (*R*)-**34** as a starting material. Enantiomeric trityl derivatives of glycerol (**33**) were used for convenient preparation of unsaturated lipids[43,44] (Scheme 8).

Saturated lipids can be obtained in a much simpler way by starting from benzyl derivative (*S*)-**19**, as shown in Scheme 9.[42–46]

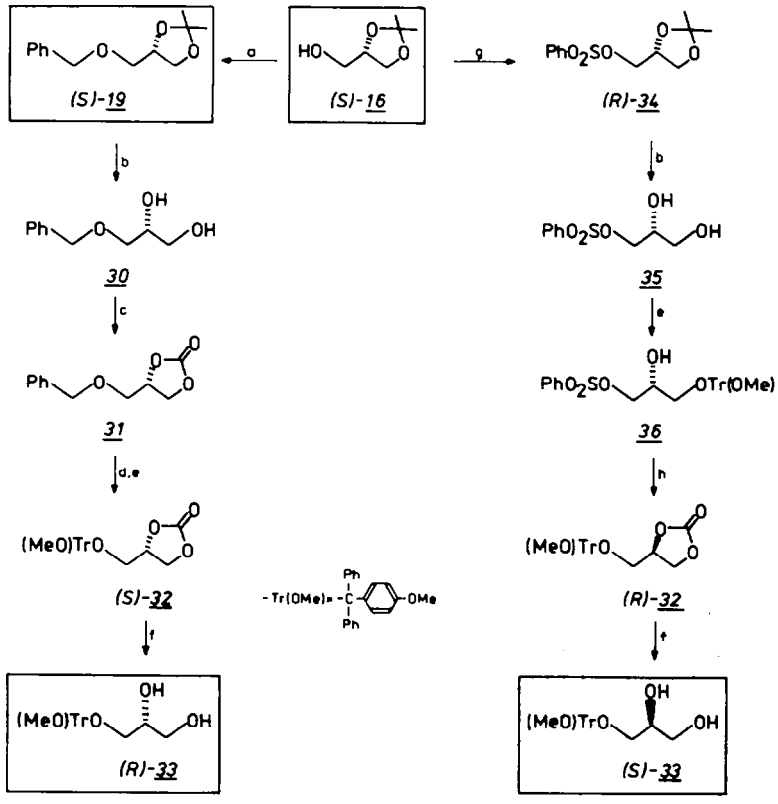
Benzyl derivative (*S*)-**19** was also used as a starting compound in the synthesis of diphosphines, applied as chiral ligands of rhodium catalysts for asymmetric hydrogenation[47,48] (Scheme 10).

(*R*)-1,2-Bis(diphenylphosphino)-3-(benzyloxy)propane (**44**) was obtained in 50% overall yield. The key step of the synthesis, i.e. nucleophilic displacement of the *p*-toluenesulfonate groups of **43** with diphenylphosphide anion, gave optically pure ligand (*R*)-**44**. Hydrogenolysis of **44**, to obtain phosphine alcohol **50**, under a variety of conditions failed to afford the expected product. Therefore, the synthesis of chiral 1,2-diphosphines **49** and **50** (with a reactive OH group) was performed in another way. Compound (*S*)-**16** was converted into 1-benzyl derivative **45** which in turn was hydrolyzed and tosylated to give **46**. Since the benzoate group in **46** is unstable to nucleophiles, it was necessary to replace it before sodium diphenylphosphide treatment. Therefore, after hydrolysis, the resulting **47** was allowed to react directly with isobutylene to yield **48**. The displacement reaction afforded diphosphine **49** which treated with trifluoroacetic acid produced (*R*)-1,2-(diphenylphosphino)propan-3-ol (**50**).

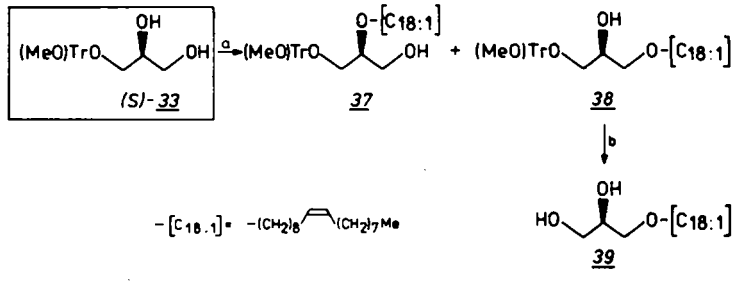
(*R*)-γ-Benzyloxymethyl-γ-butyrolactone derivatives, valuable intermediates in the synthesis of various optically active natural products including carbohydrates, terpenes and alkaloids, could also be prepared from (*S*)-**19**[41,49,50] (Scheme 11).



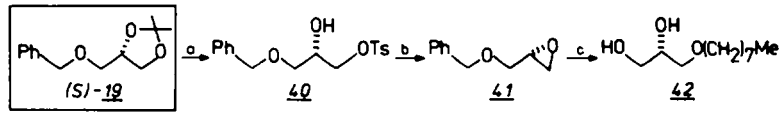
Scheme 6. Reagents: (a) MsCl, Et_3N; (b) KX, 18-crown-6; (c) (i) H^+, H_2O, (ii) TsCl, pyridine; (d) base.



Scheme 7. Reagents: (a) $PhCH_2X$, NaOH, $Bu_4N^+Br^-$; (b) HCl, H_2O, dioxane; (c) $EtOCO_2Et$, NaOH; (d) H_2, Pd/C; (e) (MeO)TrCl; (f) KOH, H_2O, MeOH; (g) $PhSO_2Cl$; (h) $KHCO_3$, DMSO.

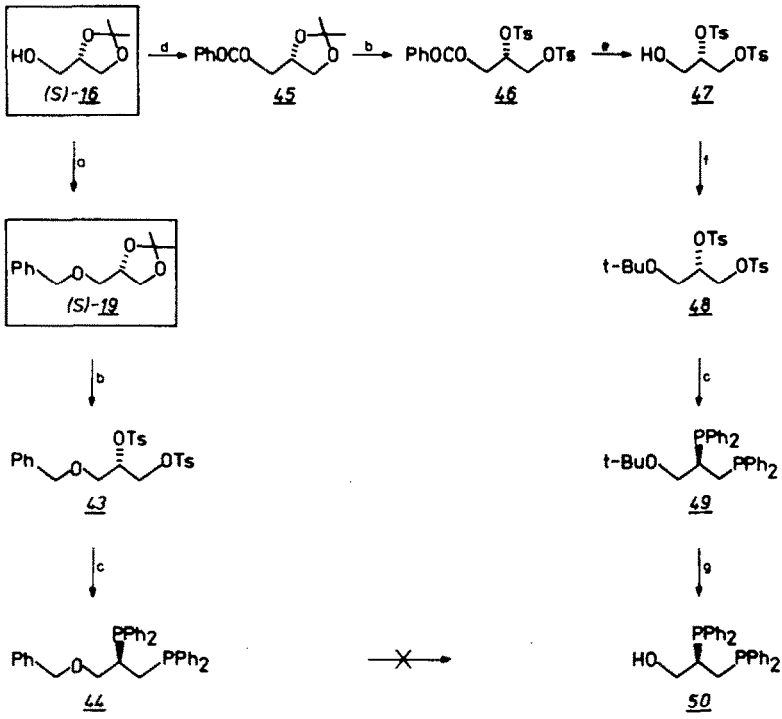


Scheme 8. Reagents: (a) (i) NaH, (ii) $C_{18:1}$-OTs, DMF; (b) HCl, H_2O, dioxane.

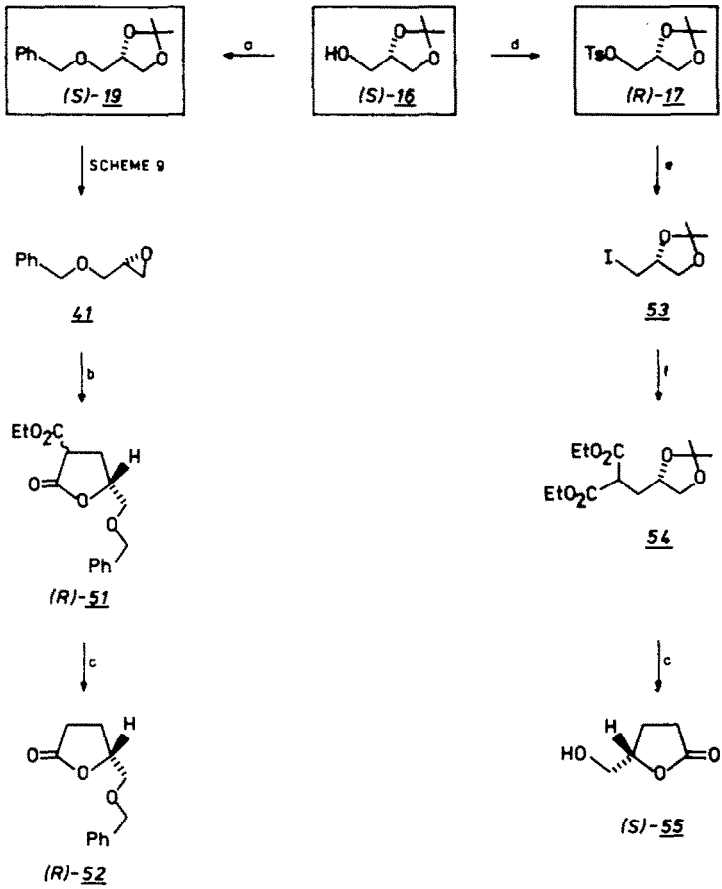


Scheme 9. Reagents: (a) (i) 1 N H_2SO_4, Me_2CO, (ii) TsCl, pyridine; (b) t-BuOK, THF; (c) (i) $Me(CH_2)_{17}OH$, NaH, DMF, (ii) H_2, Pd/C.

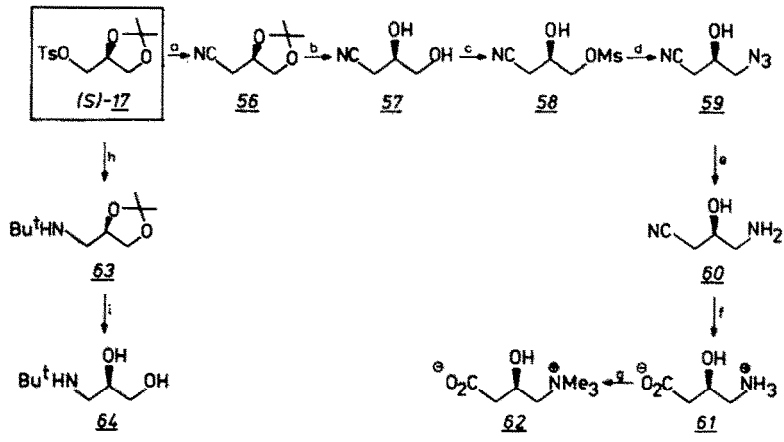
The synthesis shown in Scheme 11 consisted of a two-step sequence starting from known epoxide **41**. The reaction of **41** with diethyl malonate in ethanol in the presence of sodium ethoxide furnished the α-carbethoxy-γ-butyrolactone derivative **51** as a mixture of epimers, which refluxed with magnesium chloride in wet dimethyl acetamide was smoothly decarboxylated to give (*R*)-γ-benzyloxymethyl-γ-butyrolactone (**52**). The γ-butyrolactone derivative with the opposite configuration was obtained



Scheme 10. Reagents: (a) $PhCH_2Cl$, NaOH; (b) (i) AcOH, H_2O, (ii) TsCl, pyridine; (c) Ph_2PNa, THF; (d) PhCOCl, pyridine; (e) MeONa, MeOH; (f) isobutylene, H^+; (g) CF_3CO_2H.



Scheme 11. Reagents: (a) $PhCH_2Br$, $Et_3(PhCH_2)N^+Br^-$; (b) $CH_2(CO_2Et)_2$, EtONa, EtOH; (c) $MgCl_2 \cdot 6H_2O$, $MeCONMe_2$; (d) TsCl, pyridine; (e) NaI, Me_2CO; (f) $CH_2(CO_2Et)_2$, NaH, DMF.



Scheme 12. Reagents: (a) KCN, $KHCO_3$, NaI, DMSO; (b) HCl, MeOH; (c) MsCl, Et_3N; (d) KN_3, 18-crown-6, MeCN; (e) H_2, Pd/C; (f) H_2SO_4, H_2O; (g) MeI; (h) t-$BuNH_2$, DMSO; (j) 1 N HCl.

starting from tosylate (*R*)-**17**[51] after its conversion into iodide **53**. The reaction of iodide **53** with diethyl malonate in dimethylformamide in the presence of sodium hydride afforded alkylated product **54**, which upon treatment with magnesium chloride furnished (*S*)-γ-hydroxymethyl-γ-butyrolactone (**55**), simultaneously with spontaneous loss of the ethoxycarbonyl and acetonide group.

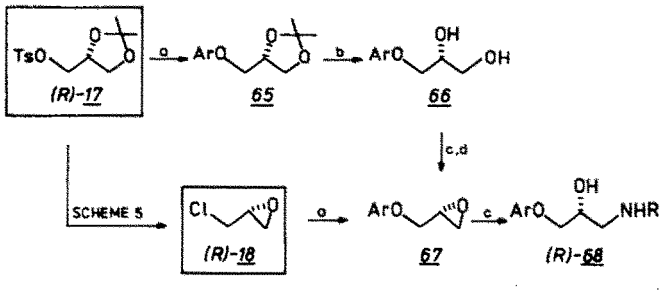
Epoxide **41** was also applied as a starting compound to the highly stereoselective synthesis of *syn*-1,3-polyols.[52]

Another example of applications of glyceraldehyde derivatives involves the synthesis of γ-amino-β-hydroxybutyric acid, starting from unnatural tosylate (*S*)-**17**[19] (Scheme 12).

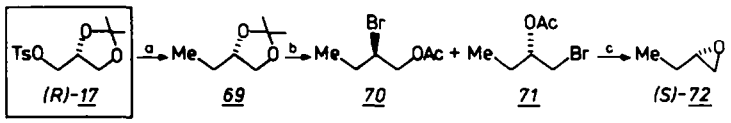
The displacement of the tosylate group in (*S*)-**17** with cyanide to produce butyronitrile **56**, followed by hydrolysis and mesylation, gave **58** which treated with potassium azide and a catalytic amount of 18-crown-6 afforded azide **59** cleanly and in good yield. Hydrogenation of **59** furnished amine **60** which was hydrolyzed to produce (*R*)-γ-amino-β-hydroxybutyric acid (**61**). Methylation of **61** under basic conditions afforded (−)-carnitine **62** (vitamin B_T).[53] Treatment of tosylate (*S*)-**17** with t-butylamine in dimethylsulfoxide produced the corresponding amine **63** which upon acidic hydrolysis furnished (*R*)-aminodiol **64**, an intermediate in the synthesis of the inactive enantiomer of important hypotensive β-adrenergic blockers.[17] The (*S*)-enantiomer of **64** was used for preparation of active (*S*)-aryloxypropanolamines.[7,54,55] Another approach to the synthesis of aryloxypropanolamines, based on (*R*)- or (*S*)-tosylate **17**, is presented in Scheme 13.

The (*R*)-enantiomer of tosylate **17** was transformed via aryloxypropylene oxide **67**[55,56] into the inactive (*R*)-enantiomer of **68**.[57–61] By application of the reaction sequence shown in Scheme 13 (displacement with aryloxide, hydrolysis, tosylation, epoxide formation and opening with an amine) to (*S*)-tosylate **17**, active (*S*)-aryloxypropanolamines could be prepared.[19] The alternative synthesis of β-adrenergic blockers of the type of **68** is possible when starting from propylene epichlorohydrin **18**.[62–64]

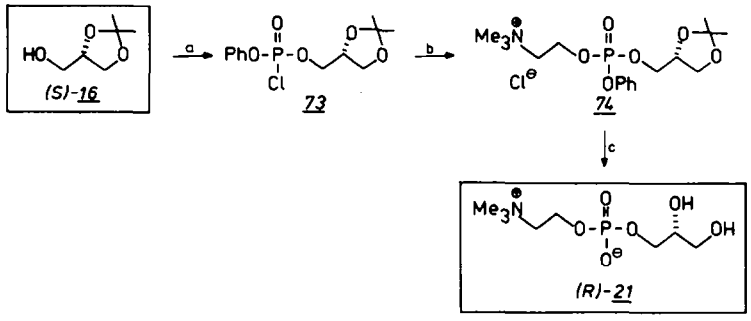
Tosylate **17** was successfully used for synthesizing the chiral 2,3-dihydroxypropyl derivatives of purine and pyrymidine bases.[65] It also found use in substitution reactions with carbon nucleophiles,[66] as shown in Scheme 14.



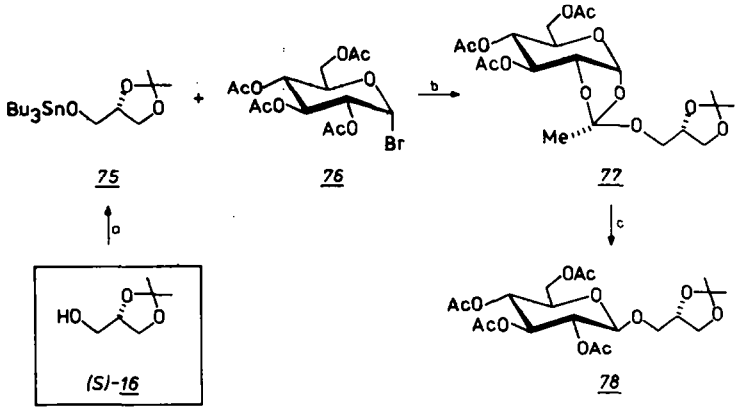
Scheme 13. Reagents: (a) ArOH, NaOH; (b) H^+, H_2O; (c) RNH_2.



Scheme 14. Reagents: (a) MeLi, CuI, Et_2O; (b) HBr, AcOH; (c) n-$C_5H_{11}OK$, n-$C_5H_{11}OH$.



Scheme 15. Reagents: (a) $PhOPOCl_2$, quinoline; (b) $HOCH_2CH_2N^+Me_3Cl^-$, pyridine; (c) (i) H_2, Pt, (ii) H^+, H_2O, pH 1.5–2.5.



Scheme 16. Reagents: (a) $(Bu_3Sn)_2O$ toluene; (b) $Et_4N^+Br^-$, $ClCH_2CH_2Cl$; (c) $HgBr_2$.

Tosylate (*R*)-**17** reacted with methyllithium stereoselectively to give dioxolane **69** in which the tosyl function was replaced by an alkyl group. From **69**, oxirane (*S*)-**72** was obtained in high optical yield.

Chiral **21** is a key synthon for the synthesis of lecithins.[67–70] It was conveniently obtained by the path presented in Scheme 15.[67,68]

Phosphorylation of (*S*)-**16** with phenylphosphonyl dichloride in the presence of quinoline, followed by esterification of the reaction product **73** with choline in the presence of pyridine, afforded isopropylidene-glycerphenyl-phosphoryl-choline chloride **74**. Finally, the protective phenyl and acetonide groups were removed by hydrogenation and hydrolysis, respectively.

2,3-O-Isopropylideneglycerol (**16**) serves also as a starting material for preparation of glycosyl glycerides;[71–73] one of these applications is shown in Scheme 16.[71]

In order to obtain the derivatives of 1-O-α-D-glucopyranosyl-D-glycerol, the direct orthoester approach using tributyltin alkoxide was applied.[71] A stoichiometric mixture of 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide **76** and (*R*)-2,3-O-isopropylidene-1-O-(tributyltin)-glycerol **75** (readily prepared from (*S*)-**16**) in 1,2-dichloroethane in the presence of added tetraethylammonium bromide gave stereospecifically *exo*-orthoester **77** in 87% yield. Subsequent treatment of **77** with mercuric bromide, without solvent, afforded the rearranged 1,2-*trans*-D-glucoside **78** in 75% yield.

Apart from the above-mentioned transformations, applications of 2,3-O-isopropylideneglycerol derived from both enantiomers of glyceraldehyde, via alkylation[42–44] or acylation[74] leading to unnatural monoglycerides were reported. Preparations of *sn*-glycerol-3-phosphates[2,75] and chiral macrobicyclic polyethers[76] also utilize **16** as a starting material.

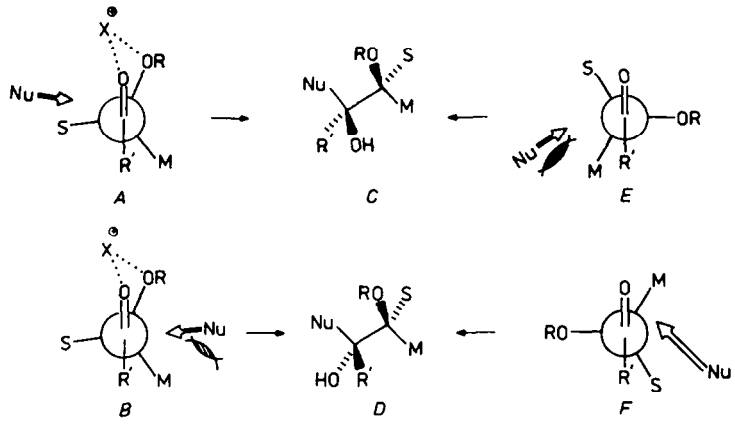


Fig. 3.

4. NUCLEOPHILIC ADDITIONS AND RELATED REACTIONS

4.1. *Stereochemical model considerations*

Addition of nucleophilic agents to the carbonyl group is a very important reaction in organic chemistry.[77] When carbon nucleophiles are used, a new C—C bond and a hydroxyl group are simultaneously formed. In case of the formation of a secondary or a tertiary alcohol, a centre of chirality is created on the carbon atom derived from the prochiral carbonyl group. Differentiation of faces of the C=O group may occur under the following circumstances: 1° influence of a chiral grouping present in the carbonyl compound, 2° addition of the nucleophilic chiral reagent, and 3° simultaneous action of both former factors.

As concerns 2,3-O-isopropylideneglyceraldehyde (1) bearing a centre of chirality in position α with respect to the formyl group, the circumstances referred to in 1° and 3° are possible. The majority of applications of 1 in organic synthesis takes advantage of its chirality for differentiation of the faces of the C=O group (cf 1°). This is consistent with the contemporary tendency for maximal utilization of the influence of centres of chirality present in starting compounds, when forming new ones.[78] Reactions in which the stereochemical outcome is determined by interplay of factors (as defined in 3°) were studied less frequently (see aldol condensation).

The relationship between the direction of addition of the nucleophilic reagent to the carbonyl group, and the reagent structure and reaction conditions continues to be an object of extensive studies. Attempts were made to rationalize the results by proposing various models of diastereoisomeric transition states describing substrate–nucleophile interactions.[79–84] Detailed discussion of the models proposed exceeds the range of this review; it was presented exhaustively by other authors.[1] However, we shall briefly consider two of them: Cram's "cyclic" model[80] and that of Cherest *et al.*[83] as modified by Nguyen Trong Anh and Eisenstein.[84] These models are selected on account of their suitability for an analysis of the reaction of (*R*)-1 with nucleophilic reagents.

Cram's "cyclic" model (Fig. 3) was proposed for carbonyl compounds with an alkoxyl group in position α with respect to the aldehyde or ketone functionality. The model assumes coordination of the cationic fragment (X^+) of the nucleophilic reagent by O atoms, fixing the periplanar conformation of the carbonyl compound. This permits two approaches of nucleophile (Nu) to the C=O plane: A and B, as indicated in Fig. 3. Approach A is more favoured, owing to weaker steric interactions between a nucleophile Nu and substituent S. Therefore, product C with *syn*[85] relation of both oxygen-containing substituents ought to be the main component of the mixture of diastereoisomers formed. As a result of the less favoured approach B, the second diastereoisomer D (*anti*[85]) ought to be formed in a smaller amount.†

Cherest *et al.*'s model[83] neglects the coordinating action of X^+ and stresses nonbonding interactions of approaching atoms. As a result, the alkoxyl group being a large substituent (OR = L) is

† The nomenclature "anti–syn" describing relative stereochemistry of two neighbouring chirality centres is consequently used throughout this report.

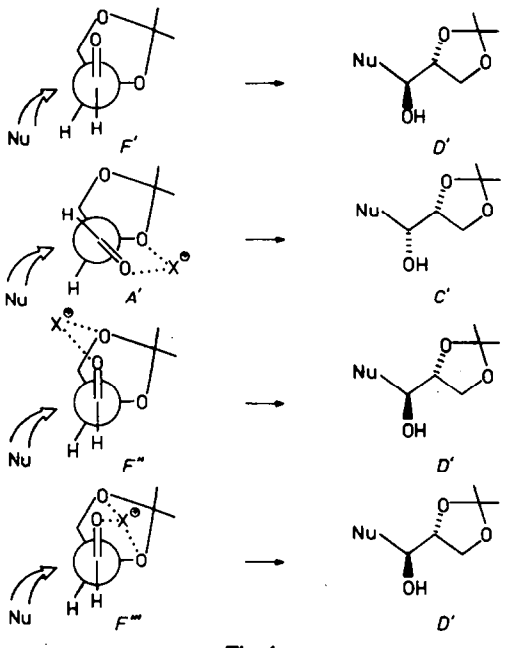


Fig. 4.

assumed to be arranged perpendicularly to the carbonyl group (Fig. 3). The nucleophile may attack the C=O bond in two most favoured conformations denoted as projections E and F. Upon assumption of interactions between Nu and S or M, being analogous to those in Cram's model, approach F as compared with approach E is preferred. As a result, product D of *anti* relation ought to be formed as the predominant diastereoisomer. Therefore, both models assume different transition states leading to opposite diastereoisomers as main products: isomer *syn* (C) in the case of Cram's "cyclic" model and isomer *anti* (D) in Cherest *et al.*'s model.

(*R*)-2,3-O-Isopropylideneglyceraldehyde (1) differs from simple α-alkoxycarbonyl compounds in that it contains a rigid dioxolane system. If cation coordination plays an important role in a nucleophile addition process it can be assumed that both heterocyclic oxygen atoms of (*R*)-1 participate in fixation of the respective conformation in the transition state.

Figure 4 presents the models proposed for nucleophile addition to the formyl group of (*R*)-1.[86,87] Model F′ is a variant of Cherest *et al.*'s model, analogous to F; it assumes formation of a mixture, with predominance of stereoisomer *anti* (D′). In the case of complexing interactions with the cationic fragment of the nucleophile (X^+), three models of transition state A′, F″ and F‴ were proposed (Fig. 4). Model A′ is identical with Cram's "cyclic" model A. Coordinating interactions involve only the oxygen atoms of the carbonyl group and of the α-alkoxy group; it postulates preponderance of isomer *syn* (C′ — analogue of C). Models F″ and F‴ assume the possible participation of the "β-alkoxyl" oxygen atom in coordinating interactions with X^+. In model F″, complexation does not include the "α-alkoxyl" O atom, and in model F‴ all three O atoms of (*R*)-1 interact with the cation. In both cases, the conformation of (*R*)-1 is very similar to that proposed in Cherest *et al.*'s model F′. Consequently, the attack of the nucleophile from the least hindered face should yield product D′ with *anti* configuration. Comparison of the transition states A′, F″ and F‴ indicates that the conformation of (*R*)-1 may be fixed by interaction with X^+ within a range limited, on the one hand, by A′ and, on the other, by F″. It is noteworthy that continuous transition from interactions $O_{C=O}^{\cdots\cdots}X^+ \ldots O_\alpha$ (A′) through $O_{C=O}^{\cdots\cdots}X^+ :: O_\alpha$ (F‴) to $O_{C=O}^{\cdots\cdots}X^+ \ldots O_\beta$ (F″) is possible.[88] Another approach to the above-mentioned transition states is shown in Fig. 5.[88]

It seems that model *F″ represents the most favourable state energetically, owing to the presence of the pseudo-chair conformation of the six-membered ring of the chelate. As compared with model *F″, the energy of *F‴ ought to be higher on account of the pseudo-boat conformation, similarly as the energy of *A′ containing a rigid five-membered ring of chelate. Since models *F″ and *F‴ lead to predominance of isomer *anti*, it can be assumed that in the reactions of 2,3-O-isopropylideneglyceraldehyde with nucleophiles, in which the cation may interact with O atoms of 1,

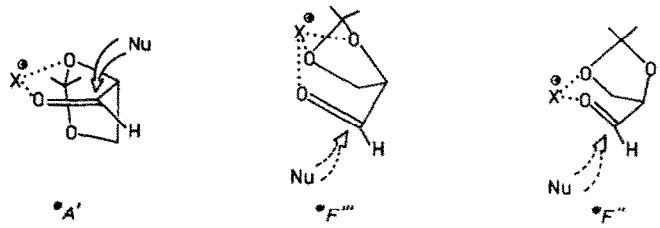


Fig. 5.

isomer *anti* should always predominate. Isomer *anti* is also predicted to be the main one by Cherest *et al.*'s model F' (Fig. 4) describing the reaction in which there are no complexing interactions between X^+ and O atoms of the carbonyl compounds.

In agreement with the above considerations,[88] the reactions of **1** with nucleophilic reagents predominantly give the *anti* isomer.[86,87] This conclusion is inconsistent with the results of Still and McDonald,[89] concerning the Grignard reaction with α-alkoxyaldehydes.

4.2. *Additions of metalloorganic reagents*

Reactions of 2,3-O-isopropylideneglyceraldehyde (**1**) with metalloorganic reagents were widely studied. Mulzer and Angermann[86] performed systematic studies of the relationship between stereoselectivity of addition and structure of a nucleophile (Table 1).

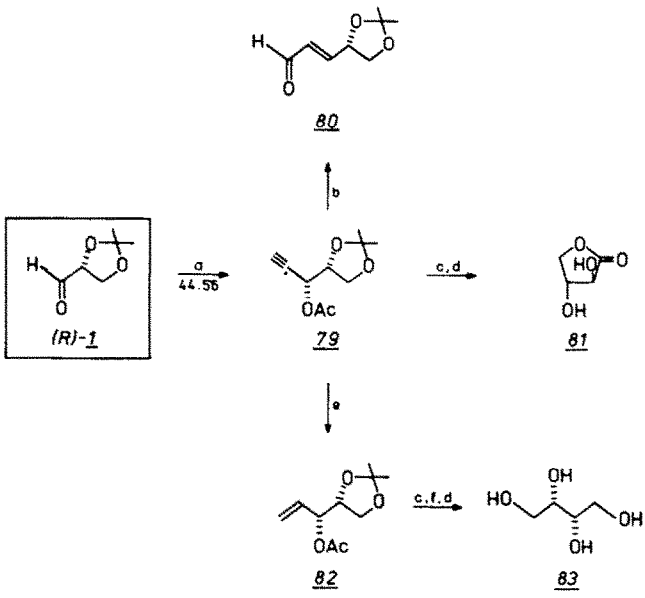
Upon use of lithioorganic compounds and Grignard reagents, low or medium stereoselectivity was observed (Table 1, entries 1, 2, 6–9 and 11), in agreement with earlier results from Japanese authors.[25] Application of titanium- and zincorganic compounds greatly improved selectivity, yielding products *anti* in a 9 : 1 ratio (entries 10 and 15, respectively). All reagents favoured formation of isomer *anti*, except for phenyltriisopropoxytitanium which afforded isomer *syn* with very high selectivity (entry 5) presumably, the only instance of so high a *syn*-selectivity in the reaction of a nucleophilic reagent with (*R*)-**1**. Moreover, an increase in selectivity occurred upon change of solvent from ethyl ether to tetrahydrofuran (entries 4, 5 and 14, 15). Other authors[90] obtained strikingly high *anti*-selectivity (95 : 5), carrying out the reaction of Grignard reagent $CH_2{=}CH(CH_2)_5MgBr$ with (*R*)-**1** in a tetrahydrofuran–hexamethylenephosphotriamide mixture at −70°; however, these authors did not comment on their results.

Potential utility of the products of metalloorganic reagents' additions to (*R*)-**1**, as starting substances for further syntheses, was noticed relatively early. Horton *et al.*[91] studied ethynylation of (*R*)-**1** with the use of Grignard reagent, observing slight predominance of isomer *syn* (Scheme 17).

A mixture of stereoisomeric acetates **79** was transformed into α,β-unsaturated aldehyde **80** by hydroboration.[92] The separated, optically pure acetates were converted to the respective lactones (acetate **79** into threonolactone **81**). Acetate **79** was also transformed, after selective hydrogenation, into olefin **82** which in turn gave threitol **83**.

Table 1. Stereochemistry and yields for various RM-addition to (*R*)-**1**

Entry	R	M	Solvent/temp (°)/ time (hr)	Yield (%)	*anti* : *syn*
1	Ph	Li	Et_2O/−78/2	88	48:52
2	Ph	MgBr	Et_2O/−78/2	85	48:52
3	Ph	$Zn_{1/2}$	Et_2O/−40/2	46	79:21
4	Ph	$Ti(Oi\text{-}Pr)_3$	Et_2O/−78/2	82	24:76
5	Ph	$Ti(Oi\text{-}Pr)_3$	THF/−78/2	79	9:91
6	Me	Li	Et_2O/−70/2	60	60:40
7	Me	MgBr	Et_2O/−50/2	57	67:33
8	nBu	Li	Et_2O/−78/2	83	69:31
9	nBu	MgBr	Et_2O/−78/2	86	75:25
10	nBu	$Ti(Oi\text{-}Pr)_3$	Et_2O/22/12	40	90:10
11	allyl	MgBr	Et_2O/−78/2	89	60:40
12	allyl	$Ti(Oi\text{-}Pr)_3$	THF/−100/2	72	71:29
13	allyl	$Cr_{1/2}$	THF/25/2	56	70:30
14	allyl	$Zn_{1/2}$	Et_2O/−78/2	60	84:16
15	allyl	$Zn_{1/2}$	THF/−78/2	65	91:9



Scheme 17. Reagents: (a) (i) CH≡CMgBr, THF, (ii) Ac_2O; (b) (i) $HB(CH_2CH_2CHMe_2)_2$, (ii) H_2O_2; (c) O_3; (d) H^+, H_2O; (e) H_2, $Pd/BaSO_4$; (f) $NaBH_4$.

Walton[93] reported that the reaction of vinylmagnesium chloride with (*R*)-**1** afforded an isomeric mixture with predominance of the *anti* product; the isomers separated at the stage of allyl alcohol **84** were transformed into erythrose **85** and threose (Scheme 18).

Mukaiyama and co-workers[94–96] published several papers describing the use of various metalloorganic compounds in reactions with (*R*)-**1** and (*S*)-**1**; the reaction products were usually converted to monosaccharides or their derivatives. Addition of a tribromomethyltin derivative generated *in situ* by treatment of (*R*)-**1** and carbon tetrabromide with tin(II) fluoride in dimethylsulfoxide afforded a diastereoisomeric mixture with moderate selectivity[94] (Scheme 19).

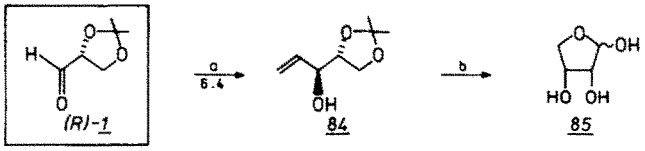
A mixture of acetate **86** and its *syn* isomer was transformed into a mixture of acetate derivatives of *threono*- and *erythrono*-lactone; the latter **87** was isolated by distillation. The reaction of allyltin difluoroiodide generated *in situ*, analogously as described in Scheme 19, afforded—after treatment with phenoxyacetyl chloride—a diastereoisomeric mixture of *anti* ester **88** and its *syn* isomer. Subsequently, the major isomer *anti* **88** was transformed into 2-deoxyribose **89** in three steps[95] (Scheme 20).

The cadmoorganic reagents obtained *in situ* from 2-allyloxybenzymidazole (**90**) reacted with (*R*)-**1** to give a mixture of regioisomers **91** and **92** in 89:11 ratio.[95] Major isomer **91** was converted into diastereoisomerically pure epoxyvinyl compound **93**, which in turn was in a few steps transformed into D-ribose **94** (Scheme 21). An identical reaction sequence performed for (*S*)-**1** yielded L-ribose.[96]

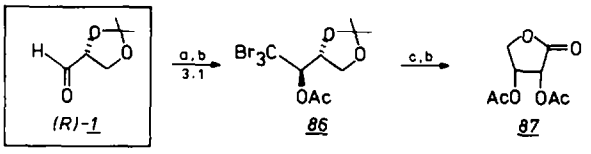
The reaction of furyllithium with (*R*)-**1** was also studied by Suzuki *et al.*[87] It was found that addition of Zn salt reversed the direction of induction, yielding in the case of ZnI_2 catalysis practically pure isomer *anti* **95**; this compound was in four steps converted into D-ribulose **96** (Scheme 22).

The reaction leading to **95** was also carried out by Dziewiszek *et al.*[97] Compound **95** was transformed by a sequence of reactions, into a mixture of methyl glycosides. The minor α-anomer **97** was converted in several steps into D-glycero-D-mannoheptose **98** (Scheme 23).

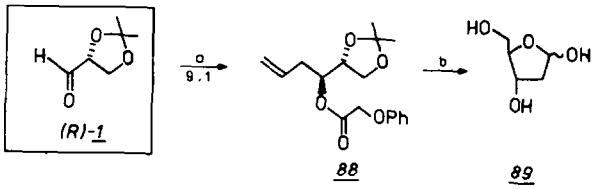
Depezay and co-workers[98] studied the reaction of the lithium derivative of acrolein diethylacetal **99** with (*R*)-**1**. They obtained a mixture of separable products: **100** and its *syn* isomer in a 7:3 ratio. Under controlled conditions of acidic hydrolysis, product **100** was transformed into 2-methyleneribose **101**,



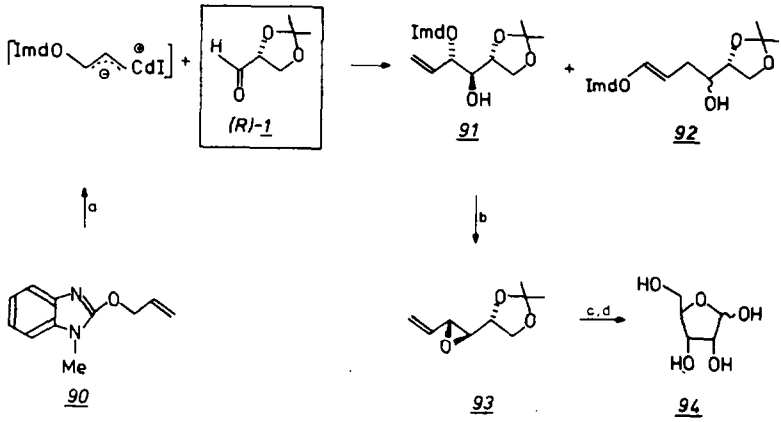
Scheme 18. Reagents: (a) CH_2=CHMgCl; (b) (i) O_3, (ii) H^+, H_2O.



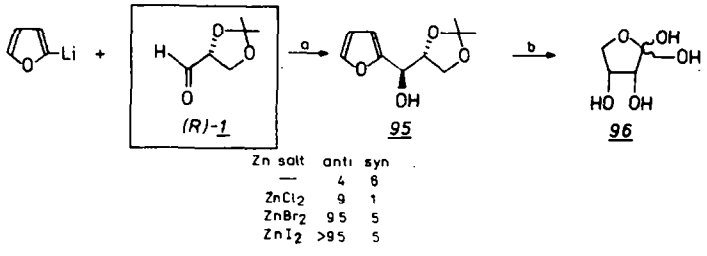
Scheme 19. Reagents: (a) CBr_4, SnF_2, DMSO; (b) Ac_2O, pyridine; (c) $AgNO_3$, H_2O.



Scheme 20. Reagents: (a) (i) $CH_2{=}CHCH_2I$, SnF_2, THF, DMF, (ii) $PhOCH_2COCl$; (b) (i) NH_4OH, (ii) AcOH, (iii) O_3, (iv) Me_2S.

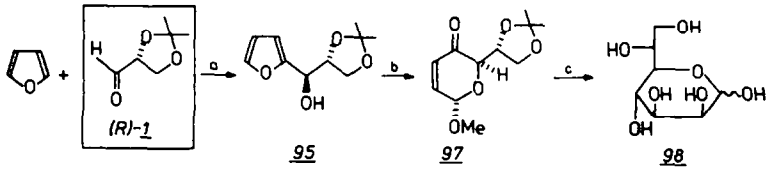


Scheme 21. Reagents: (a) (i) BuLi, (ii) CdI_2, THF; (b) NaH, THF; (c) BuOH, neutral Al_2O_3, Et_2O; (d) (i) O_3, (ii) Me_2S, (iii) SiO_2 chrom., (iv) H_2, Pd/C.

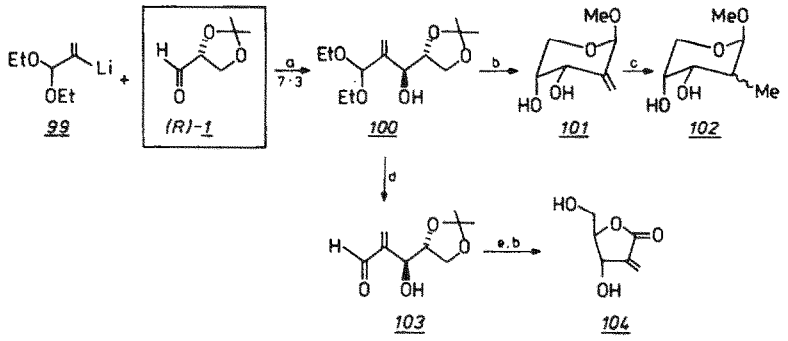


Zn salt	anti	syn
—	4	6
$ZnCl_2$	9	1
$ZnBr_2$	95	5
ZnI_2	>95	5

Scheme 22. Reagents: (a) THF; (b) (i) Br_2, MeOH, (ii) O_3, (iii) $NaBH_4$, (iv) 2 N HCl.



Scheme 23. Reagents: (a) $ClCH_2CO_2H$; (b) (i) Br_2, MeOH, (ii) H^+, (iii) MeI, Ag_2O; (c) (i) $NaBH_4$, (ii) OsO_4, (iii) H^+.



Scheme 24. Reagent: (a) THF; (b) HCl, MeOH; (c) H_2, Pd/C; (d) HCl, THF; (e) $AgNO_3$.

and then into a mixture of 2-deoxy-2-methylriboses **102**. Compound **100** was also converted into aldehyde **103**, from which lactone **104** was prepared (Scheme 24).

David *et al.*[99] found that addition of the lithium derivative of 2-methyl-1,3-dithiane (**105**) to (*R*)-**1** led to the exclusive formation of isomer *anti* **106** which was then transformed into monosaccharide **107** (Scheme 25). The stereochemical outcome of a similar reaction employing 1,3-dithiane was not exactly studied;[100] the *anti* isomer related to **106** was obtained after fractional crystallization in 58% yield.

Hoffman *et al.*[101] investigated addition of allylboronates to (*R*)-**1**. When boroorganic **108** was used, homoallyl alcohols **110** and **111** were formed in a 4 : 1 ratio. Upon use of reagent **109**, stereoselectivity greatly increased (Scheme 26).

Moreover, addition of *cis*- and *trans*-butenylboronates **112** and **113** to (*R*)-**1** was studied.[101] Upon use of **112**, almost diastereomerically pure product **114** was obtained; in the case of boronate **113**, induction was much lower. It is noteworthy that both boron reagents **112** and **113** afforded only two out of the four possible diastereoisomers. It is also of interest that a change from racemic to optically pure boroorganic reagents only slightly improved the stereoselectivity.

Shono *et al.*[102] investigated the reaction of (*R*)-**1** with electrochemically generated anions. In the case of the trichloromethyl anion, selectivity was relatively low, whereas upon replacement of one Cl atom by the methoxycarbonyl group virtually only one diastereoisomer **118** was formed (Scheme 27).

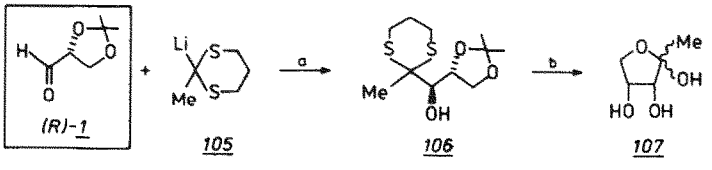
Addition products of the above-mentioned anions were utilized for the synthesis of simple derivatives of erythrose **122**, erythroulose **125**, 2-deoxyribonolactone **128**, ribonolactone **131** and lyxonolactone **132** (Scheme 28). For this purpose, also other electrochemical reactions were used.

The reaction leading to compound **126** was modified by French authors[103] who chemically generated the dichloro(methoxycarbonyl)methyl anion from methyl trichloroacetate using hexamethylenephosphoramide and magnesium chloride (Scheme 29).

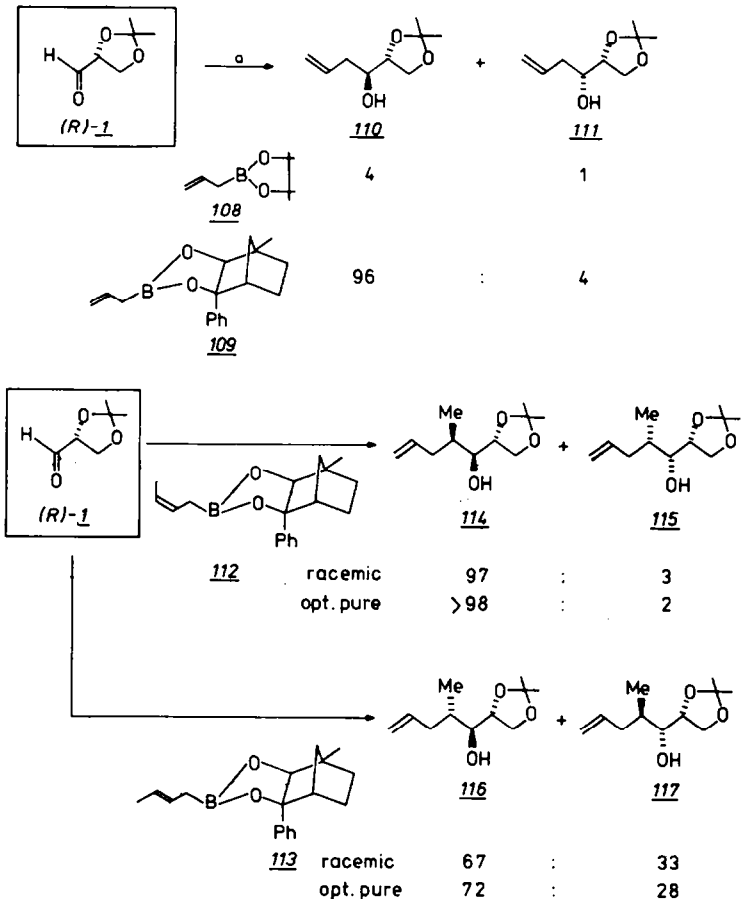
Hayon *et al.*[103] postulated formation of salts **133** and **134**; the latter reacted with (*R*)-**1** yielding **126**. Compound **126** was also obtained with 40% of *anti* selectivity in the aldol condensation of (*R*)-**1** with magnesium enolate generated from methyl trichloroacetate.[104] The stereochemical course of the reaction of (*R*)-**1** with the dichloro(methoxycarbonyl)methyl anion, and yield of olefin **135** formed as side-product depended on the amount of magnesium salt added[103] (Table 2).

Hagen *et al.*[105] investigated the reaction of (*R*)-**1** with diazomethane and sulfur ylides (Scheme 30). In all cases isomer *anti* **136** was predominant. In the reaction of (*R*)-**1** with diazomethane, a considerable amount of methylketone **138** was formed.

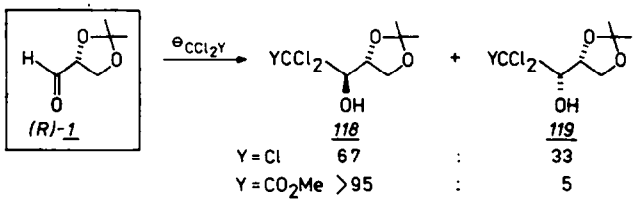
The literature furnishes a few more examples of the reaction of 2,3-O-isopropylideneglyceraldehyde (**1**) with metalloorganic reagents.[106–110] We do not discuss them, because they either fail to



Scheme 25. Reagents: (a) THF; (b) (i) HgO, $BF_3 \cdot Et_2O$, (ii) H^+, H_2O.



Scheme 26. Reagents: (a) (i) allylboronate, light petroleum, (ii) triethanolamine.



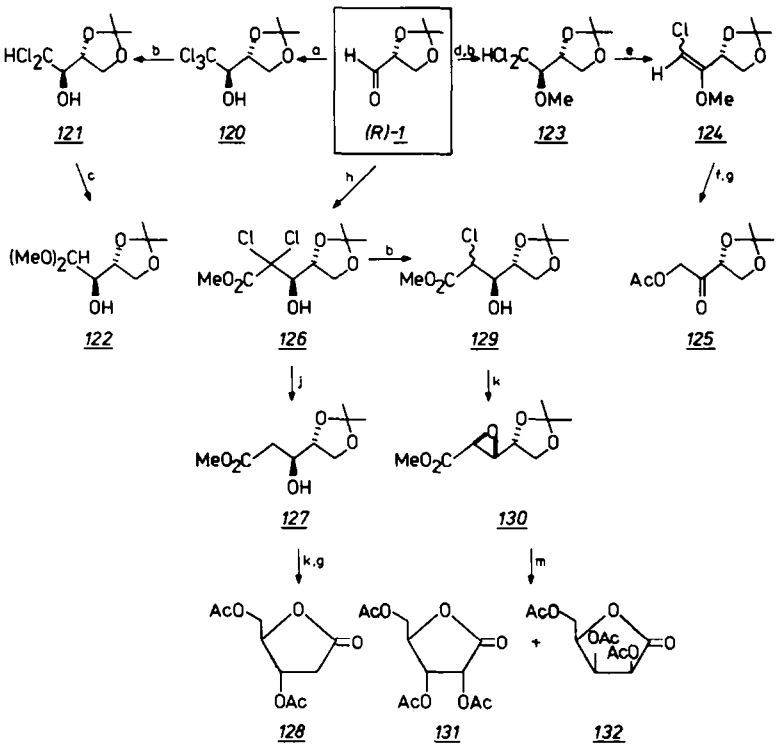
Scheme 27.

supply data concerning stereoselectivity or the newly created centre of chirality is eliminated in the further stages of synthesis.

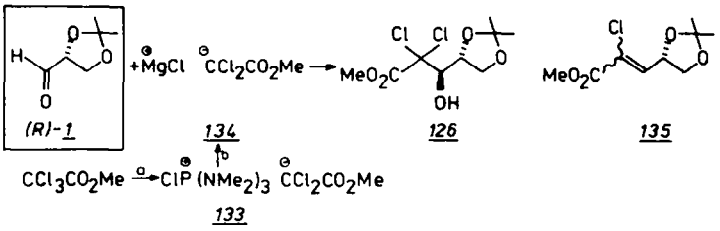
There are some interesting examples of nucleophilic addition to nitrogen analogues of (*R*)-1. Ohgo *et al.*[111] found big differences in *syn–anti* selectivity between addition reactions of phenyllithium or phenylmagnesium bromide with glyceraldimine derivatives **139** (Scheme 31). Moreover, carrying out

Table 2. Influence of $MgCl_2$ additives on the stereochemical course of the reaction shown in Scheme 29

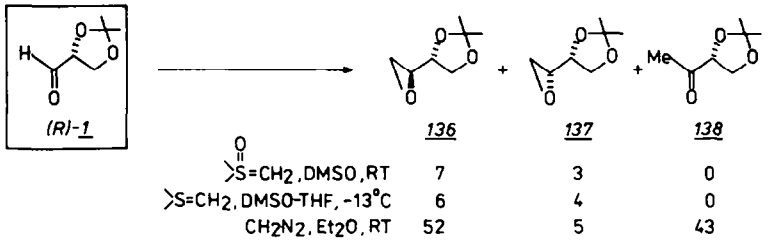
$MgCl_2$	Yield (%)	126		135
		anti	*syn*	
—	70	20	63	17
1 eq	64	71	23	6
2 eq	80	92	8	—
5 eq	66	76	24	—



Scheme 28. Reagents: (a) +*e*, CCl_4, $CHCl_3$; (b) +*e*, NH_4NO_3, MeOH; (c) KOH, MeOH; (d) NaH, MeI, THF; (e) KOH, EtOH; (f) TsOH, Me_2CO; (g) (i) NaI, Me_2CO, (ii) Ac_2O, pyridine; (h) +*e*, Cl_3CCO_2Me, Cl_2CHCO_2Me; (j) +*e*, NH_4Cl, MeOH; (k) CF_3CO_2H; (l) MeONa, MeOH; (m) (i) KOH, H_2O, dioxane, (ii) HCl, H_2O.



Scheme 29. Reagents: (a) HMPA, THF; (b) $MgCl_2$.

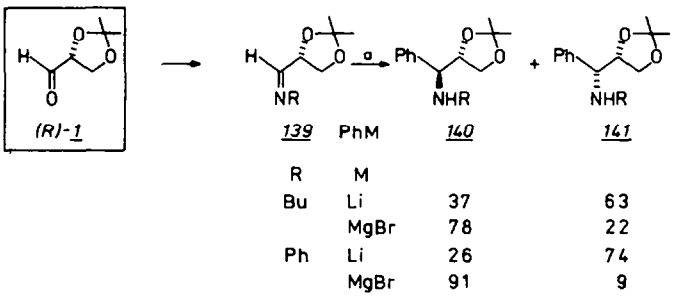


	136	137	138
$(CH_3)_2S{=}CH_2$, DMSO, RT	7	3	0
$(CH_3)_2S{=}CH_2$, DMSO-THF, -13°C	6	4	0
CH_2N_2, Et_2O, RT	52	5	43

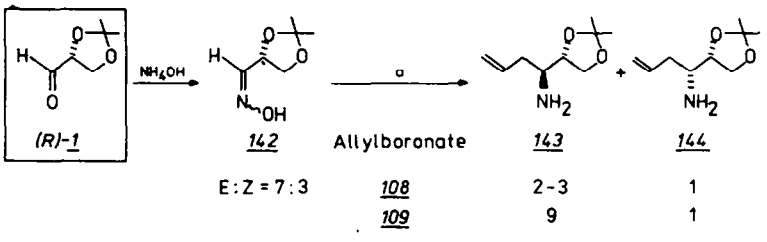
Scheme 30.

the reaction in ethyl ether, as compared with tetrahydrofuran, resulted in higher stereoselectivity, in contrast to the results obtained for (*R*)-**1**.[25]

Addition of allylboronates **108** and **109** to oxime **142** obtained from (*R*)-**1** resulted in predominance of the *anti* isomer **143**;[112] the degree of selectivity was somewhat lower than in the case of the reaction of (*R*)-**1** with **108** and **109**[101] (Scheme 32).



Scheme 31. Reagents: (a) PhM, Et_2O or THF.



Scheme 32. Reagents: (a) allylboronate, CCl_4.

4.3. *Aldol condensation and related reactions*

The renaissance of aldol condensation, observed during the past decade, resulted from the development of new methods of organic synthesis, enabling stereocontrol of the reaction course.[113,114] Application of this reaction in the total synthesis of natural products (e.g. "ansa chain" macrolides)[115] opened new synthetic pathways.

Typical directed aldol condensation involves addition of previously generated enolate **I** to carbonyl acceptor **II**, with formation of an intermediate, chelate **III**, whose hydrolysis yields the final product, aldol **IV** (Fig. 6). When chiral aldehyde **V** is used, product **VI** with two newly formed centres of chirality (carbon atoms C-2 and C-3) is obtained. These centres originate in processes involving relative asymmetric induction (centre formation on C-3 with respect to the centre on C-4) and internal one (centre formation on C-2 with respect to the centre on C-3). Factors responsible for selectivity in the relative induction were discussed in Section 4.1. Parameters controlling the degree of internal induction comprise the geometry of starting enolate (*Z* or *E*), size of substituent and reaction conditions (kinetic or thermodynamic control). These parameters were extensively studied by other authors,[113,114,116] and thus we shall only mention the main ones.

The principle of control of product stereochemistry is presented in Fig. 7. Under conditions of kinetic control, differences occur between transition states **IX** and **X** or **XI** and **XII**, depending on the enolate participating in the reaction: isomer *Z*-**VII** or *E*-**VIII**, respectively. As concerns *Z*-**VII**, transition state **IX** is favoured owing to a lack of pseudo-1,3-diaxial interactions between substituents R and R_2, this leading to isomer *syn*-**XV** as the major product. Analogically, in the case of *E*-**VIII**,

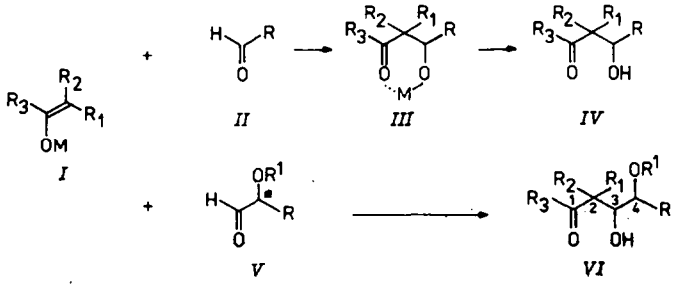


Fig. 6.

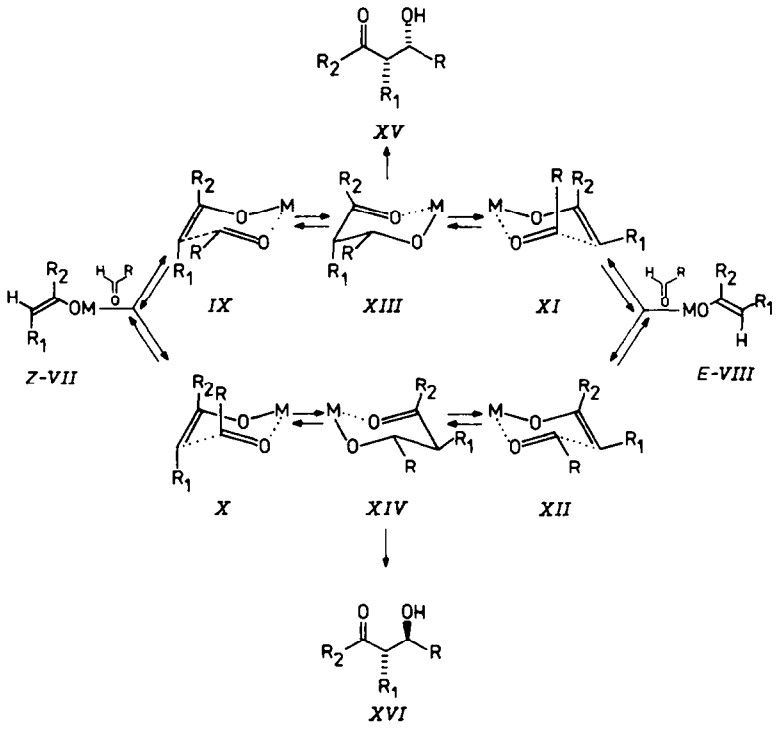


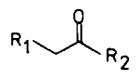
Fig. 7.

transition state **XII** is more favoured than **XI**, predominantly yielding isomer *anti*-**XVI**. It is stressed that the size of substituent R_2 in the starting enolate is the main factor controlling the degree of internal induction. Bulky substituents (e.g. t-butyl, mesityl, trimethylsilyl) result in high stereoselectivity, whereas in the case of smaller substituents (e.g. ethyl, phenyl, methoxyl) the selectivity is lower or nil. Under conditions of thermodynamic control, the *anti* isomer is predominant, irrespective of the geometry of the starting enolate. This is due to the reversibility of the process of intermediates (**XIII** and **XIV**) formation, leading to the generation of the more favourable intermediate **XIV**, with substituents R and R_1 in equatorial positions. Aldol type reactions with 2,3-O-isopropylideneglyceraldehyde (**1**) seem to be controlled by the factor discussed in this section.

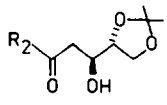
Heathcock and co-workers extensively studied aldol condensation using both (*R*)-**1** and (*S*)-**1**.[117–120] Carbonyl compounds applied as enolate precursors and the possible diastereoisomeric products are presented in Fig. 8. The results of the reaction of (*R*)-**1** with the above-mentioned carbonyl compounds are shown in Table 3.[117]

In the case of the enolate precursor of type **145**, the degree of selectivity is clearly differentiated. It is noteworthy that upon use of precursor **145a**, *anti*-**147a** was almost exclusively formed. From enolate precursors of type **146**, four diastereoisomeric products could be formed (**148a**, **b**, **c** and **d**). Product stereodistribution confirmed *anti* selectivity of 2,3-O-isopropylideneglyceraldehyde (**1**) and testified to the predominance of isomers with the *syn* relation between C-2 and C-3 (Fig. 6). For enolate precursors **146a** and **146b**, internal induction was 100%, with fairly high relative induction. In contrast, in the case of **146c**, relative induction was 100%, and internal induction dropped to about 20%. For **146d**, all four diastereoisomers occur; in this case, the direction of internal induction was opposite, as it preferred generation of isomers **148b** and **148d**.

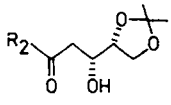
To enhance stereoselectivity of aldol condensation, Heathcock and co-workers put forward and investigated the concept of double asymmetric induction;[118,119] it involves the use of both carbonyl reagents in the optically active form. In these studies, apart from other aldehydes, (*R*)- and (*S*)-**1** were used. In the reaction with enolate obtained from the fructose derivative (**149**), both relative and internal induction greatly increased upon transition from (*R*)-**1** to (*S*)-**1** (Scheme 33), in the case of (*S*)-**1**, virtually only isomer **152** was formed. Similar results were obtained for ketone **154**, though the selectivity increased less than in the case of **146**.



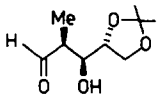
R_1 \ R_2			—OMe	
H	145a	145b	145c	145d
Me	146a	146b	146c	146d



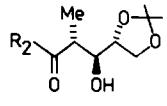
147a



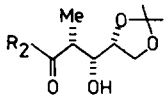
147b



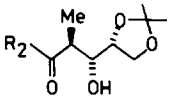
148a



148b

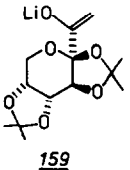


148c

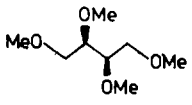


148d

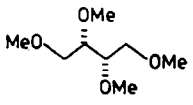
Fig. 8.



159



160



161

Fig. 9.

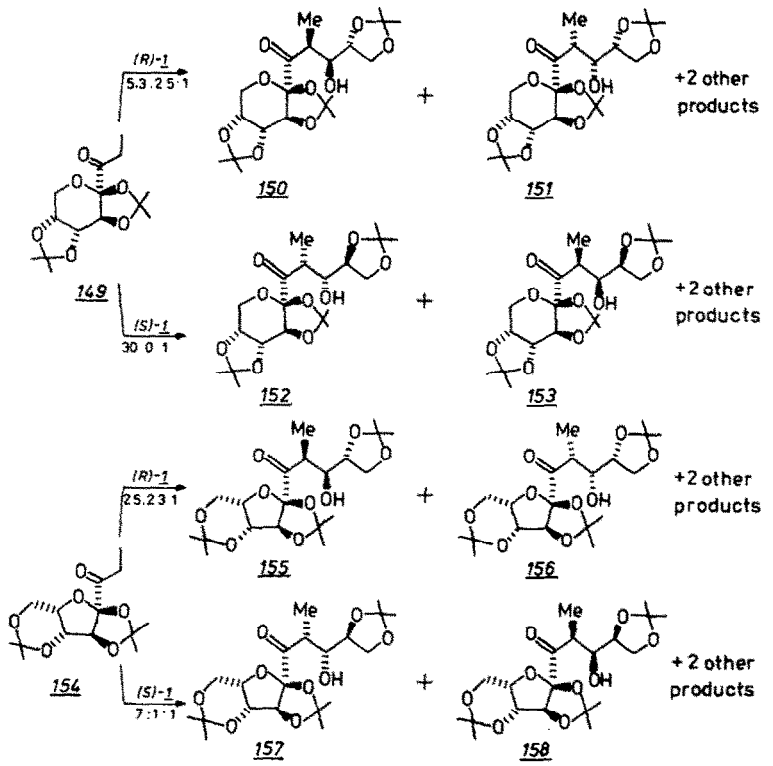
The reaction of racemic **1** with enolate **159** was characterized by absence of double stereodifferentiation. Likewise, the selectivity was not enhanced in the reaction of ketone **149** with (*R*)- and (*S*)-**1**, when the reaction was carried out in chiral solvents **160** and **161** (Fig. 9).

Furthermore, Heathcock *et al.*[120] reported that double racemic condensation of **1** with enolate **162** afforded only one stereoisomer **163** (Scheme 34).

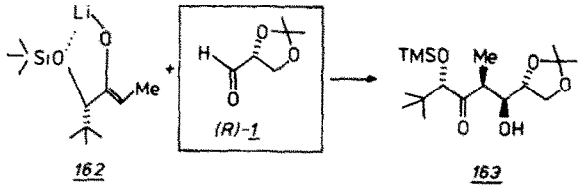
Narasaka and Pai[121] used aldol condensation to prepare hydroxyketone **164** (Scheme 35). Reduction of **164** yielded diols **165** and **166**, which after acidic hydrolysis were transformed into isomeric 3-deoxyhexoses **167** and **168**. These authors[121] used their own, highly selective method for reduction of 1,3-dihydroxyketones, with trialkylboron as chelating agent.

Table 3. Product distribution in aldol condensation of (*R*)-**1** with enolates derived from ketones **145** and **146**

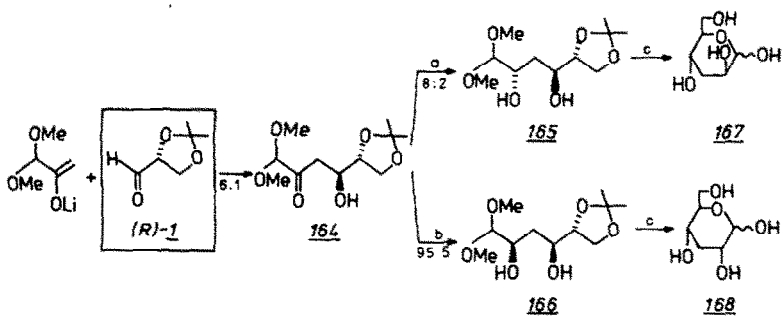
Enolate precursor	Product distribution					
	147a	**147b**	**148a**	**148b**	**148c**	**148d**
145a	>95	<5				
146a			85	0	15	0
145b	66	34				
146b			85	0	15	0
145c	85	15				
146c			60	40	0	0
145d	66	34				
146d			17	47	5	31



Scheme 33.



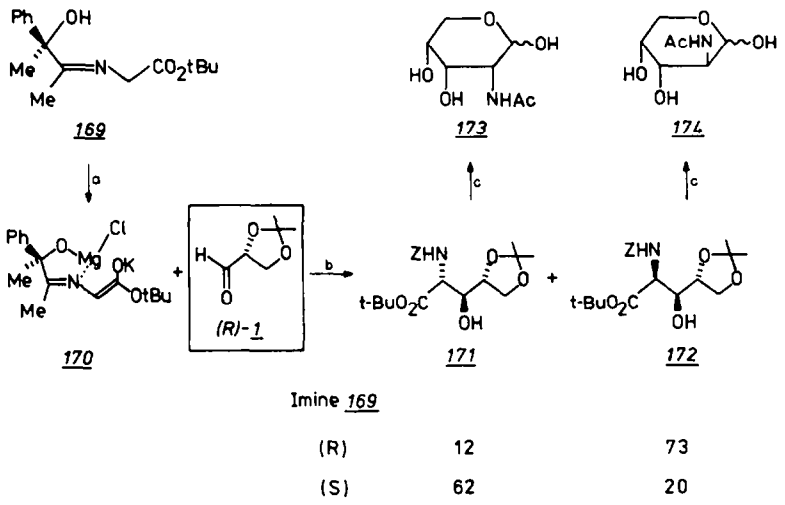
Scheme 34.



Scheme 35. Reagents: (a) $Al(Oi\text{-}Pr)_3$; (b) (i) $i\text{-}Bu_3B$, (ii) $NaBH_4$; (c) H^+, H_2O.

Mukaiyama *et al.*[122] applied imine **169** as the chiral enolate precursor (Scheme 36), obtaining a mixture of four diastereoisomers. Isomer **171** or **172** predominated depending on the configuration of the chirality centre of starting imine **169**, as shown in Scheme 36. Optically pure aminoalcohols **171** and **172** were used for the preparation of sugar derivatives **173** and **174**.

A new method for generation of boron enolates, developed by Murakami and Mukaiyama, was used to carry out aldol condensation with (*R*)-**1**.[123] Boronate **173** generated *in situ* afforded a mixture of



Scheme 36. Reagents: (a) (i) n-BuMgCl, (ii) KDA, THF; (b) (i) TMSCl, (ii) SiO_2, (iii) ZCl, pyridine, (iv) Na_2CO_3, MeOH, H_2O; (c) (i) CF_3CO_2H, (ii) $Me_2(i\text{-}Pr)SiCl$, Et_3N, DMAP, (iii) DIBAL, (iv) AcOH, H_2O, THF, (v) H_2, Pd/C, (vi) Ac_2O, pyridine.

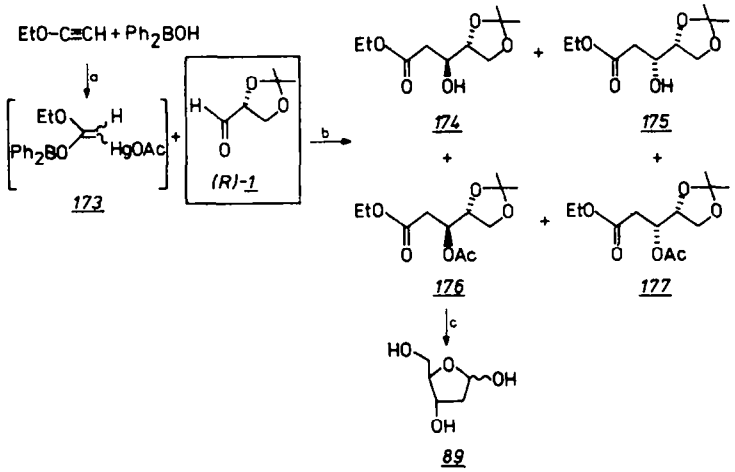
alcohols **174** and **175** as well as of their acetates **176** and **177** in a ratio of 53 : 4 : 39 : 4, respectively. After chromatographic separation, **174** and **176** were converted into 2-deoxyribose **89** (Scheme 37).

The same authors[124] utilized ethoxyacetylene for the generation of enolate **178** which was condensed with (*R*)-**1** to give epoxide **179** as a major isomer. Compound **179** was then transformed into protected 2-deoxy-2-aminoribose **182** in a seven-step reaction sequence (Scheme 38).

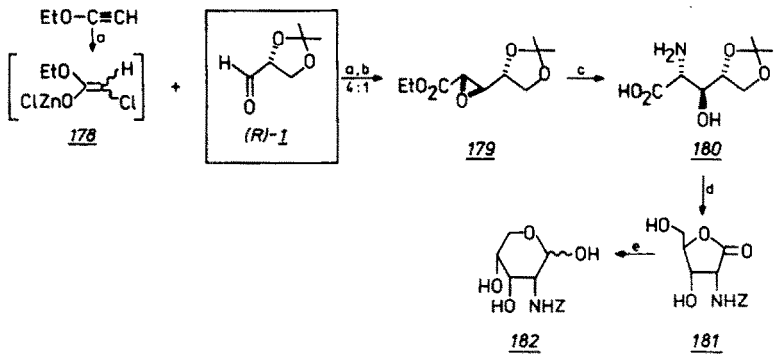
Depezay *et al.*[125] studied the reaction of the isonitrile derivative of glycine with (*R*)-**1** (Scheme 39), yielding only two *trans*-oxazolines **183** and **184**. The mixture of isomers was hydrolyzed and separated into respective formamides which were then converted to lactones **185** and **186**, and to their diastereoisomers **187** and **188**.

Hoppe and Schöllkopf[126] investigated the same reaction; the selectivity of isomer **183** formation was higher (4 : 1), when enolate was generated using butyllithium in tetrahydrofuran at −78°. Moreover, the reaction of both (*R*)- and (*S*)-**1** with the lithium derivative of piperazine (**189**) was investigated (Scheme 40).[127] In the reaction with (*R*)-**1**, there was no selectivity in the formation of the chiral centre on the carbon atom bonded with the hydroxyl group, whereas the second centre was formed with 100% selectivity. Upon use of (*S*)-**1**, diastereoisomer **191** accounting for 80% of the resulting mixture was obtained.[127]

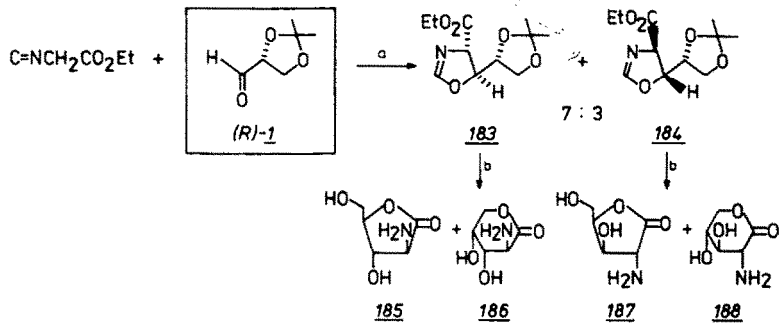
Okamoto and co-workers[128] used copper derivative **192** in the reaction with (*R*)-**1** (Scheme 41). As a result of this reaction, isomer **193** was predominantly formed; it was then transformed into 2-amino-2-deoxyxylonic acid **194**.



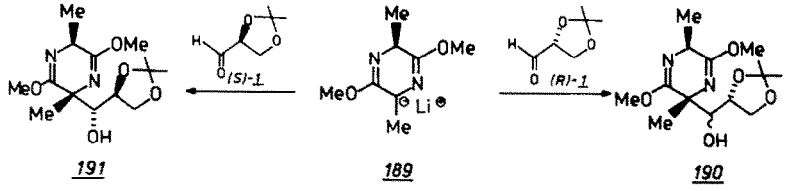
Scheme 37. Reagents: (a) $Hg(OAc)_2$; (b) THF; (c) (i) CF_3CO_2H, (ii) hexylborane, (iii) MeONa.



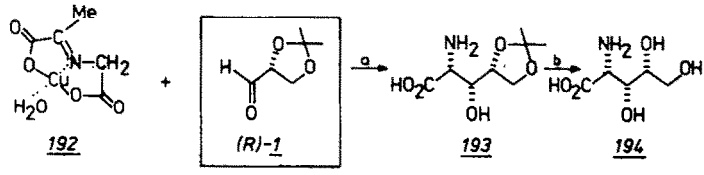
Scheme 38. Reagents: (a) pyridine N-oxide, $HgCl_2$, Zn, THF; (b) (i) H_2O, (ii) EtOLi, EtOH; (c) (i) LiOH, EtOH, H_2O, (ii) NH_3 aq; (d) (i) ZCl, $NaHCO_3$, (ii) CF_3CO_2H, H_2O; (e) (i) Me_2(i-Pr)SiCl, Et_3N, DMAP, (ii) DIBAL, (iii) AcOH.



Scheme 39. Reagents: (a) NaCN, EtOH; (b) (i) EtOH, H_2O, (ii) HCl, H_2O.



Scheme 40.

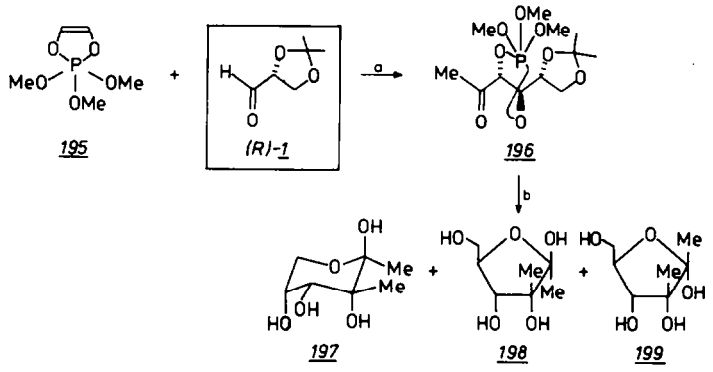


Scheme 41. Reagents: (a) (i) H_2O, pH 9.5, (ii) H_2S; (b) Amberlite IR 120B (H^+).

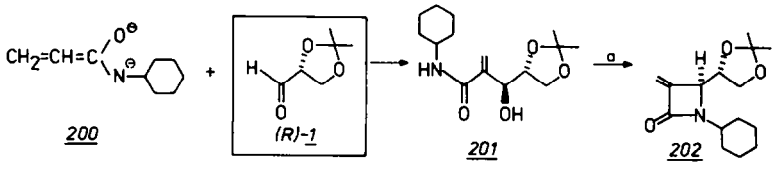
David and co-workers[129] performed Ramirez condensation, using dioxaphosphole **195** and (*R*)-**1** (Scheme 42). As the only isomer, **196** was obtained and converted into a mixture of sugar derivatives **197–199**. Similar reactions were carried out with the phenyl and tetramethylene analogue of dioxaphosphole **195**.[129]

Barrett and co-workers[130] carried out addition of diamion **200** (obtained from cyclohexylnitrile) to (*R*)-**1** (Scheme 43); the resulting product **201** was transformed into β-lactam **202**.

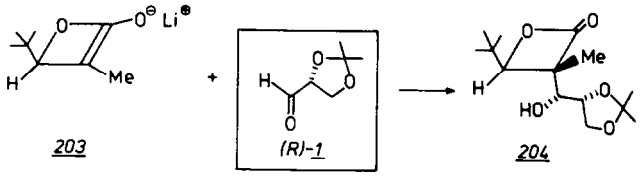
Mulzer and Chucholowski[131] investigated the reaction of (*R*)-**1** with anion **203** generated from the respective β-lactone; product **204** was obtained as virtually the only stereoisomer (Scheme 44).



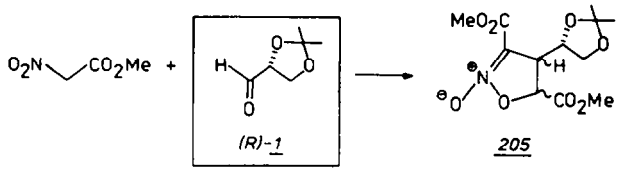
Scheme 42. Reagents: (a) benzene, (b) H^+, H_2O.



Scheme 43. Reagents: (a) BuLi, TsCl.



Scheme 44.



Scheme 45.

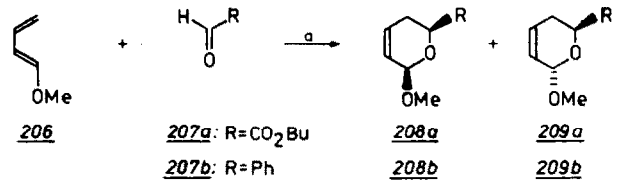
Kaji *et al.*[132] reported the formation of two *trans*-isoxazoline N-oxides **205** in the reaction of methyl nitroacetate with (*R*)-**1**, in the presence of diethylamine (Scheme 45).

Many other reported reactions of the aldol condensation type, involving 2,3-O-isopropylideneglyceraldehyde (**1**), are not discussed here, because (1) the stereochemical course of reaction was not determined, (2) the reaction yielded a racemic mixture and (3) the newly formed centre of chirality was destroyed at subsequent stages.[133–135]

5. PERICYCLIC REACTIONS

5.1. *Diels–Alder cycloaddition and related reactions*

Of the pericyclic reactions, (4 + 2) cycloaddition is used most often in organic synthesis. Owing to the multitude of dienes and dienophiles, it is possible to obtain variously functionalized adducts—starting compounds for the syntheses of many important natural products.[136] Heterodiene synthesis of 1-methoxybuta-1,3-diene (**206**) with activated carbonyl compounds (e.g. butyl glyoxylate **207a**) as dienophiles, yielded derivatives of 5,6-dihydro-2H-pyran: *cis*-**208a** and *trans*-**209a**, in the form of racemic mixtures[137] (Scheme 46).



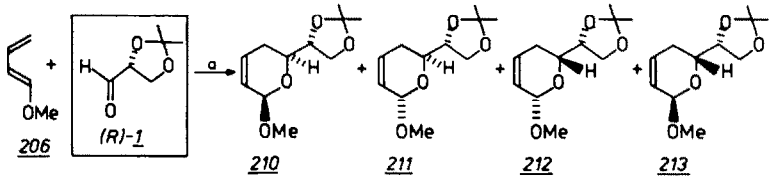
Scheme 46.

In the case of nonactivated dienophiles, heterodiene synthesis fails to proceed under thermal conditions, even with as reactive a diene as **206**. However, the use of a high-pressure technique enables this reaction to be carried out. The Diels–Alder reaction exhibits a negative volume of activation $\Delta V^{\neq}$, i.e. the volume occupied by the transition state is smaller than that occupied by the reactants, and consequently the reaction is strongly pressure accelerated.[138] In the reaction of diene **206** with benzaldehyde (**207b**), carried out under 19.5 kbar pressure at 50° for 5 hr, a mixture of racemic adducts *cis*-**208b** and *trans*-**209b** was obtained in 80% yield (Scheme 46); under high-pressure conditions, *endo*-addition yielding the *cis*-isomer was strongly preferred.[139] The high-pressure approach to heterodiene synthesis offers a very convenient and efficient method for the preparation of various substituted derivatives of 5,6-dihydro-2H-pyran, not readily—if at all—obtainable by other procedures. Diels–Alder reactions exemplified in Scheme 46 were applied in total syntheses of monosaccharides,[137] biologically active lactones[140] and other natural products.[136,141]

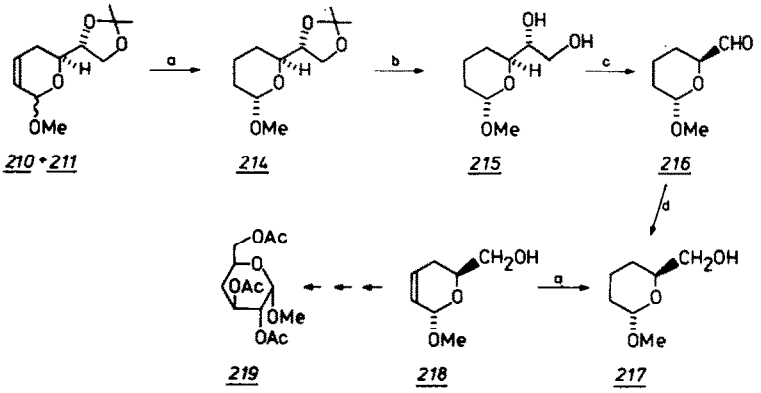
The use of chiral aldehydes, particularly of 2,3-O-isopropylideneglyceraldehyde (**1**), opens up a wide range of new possibilities to carry out stereocontrolled transformations leading to optically active compounds.[142,143] Cycloaddition of (*R*)-**1** to diene **206** gives rise to chiral cycloadducts (Scheme 47). When the reaction was carried out under high-pressure conditions four diastereoisomeric adducts were formed: two *cis* diastereoisomers (**210** and **212**), by *endo* addition, and two *trans* diastereoisomers (**211** and **213**) by *exo* addition, in the proportion of 66:16:13:5, respectively[143] (Scheme 47).

The direction of asymmetric induction was determined by chemical correlation of the (**210**+**211**) mixture with **217** which has a known absolute configuration (having been correlated with natural sugar **219**). This correlation[143] is presented in Scheme 48.

High-pressure conditions enabled this cycloaddition, which could not be performed under



Scheme 47. Reagents: (a) diethyl ether, 22 kbar, 50°.



Scheme 48. Reagents: (a) H_2, Pt; (b) 1% HCl, MeOH; (c) $NaIO_4$; (d) $LiAlH_4$.

Table 4. Influence of pressure on asymmetric induction in the cycloaddition of (*R*)-1 to **206**

Entry	Solvent†	*P* (kbar)	*T* (°)	Yield (%)	Diastereoisomeric composition (%) 210	211	212	213	*cis*:*trans* ratio (210+212):(211+213)	d.e. (*endo*) (%)	d.e. (*exo*) (%)
1	A	14.5	50	42	63.0	15.5	15.0	6.5	78:22	61.5	40.9
2	A	18.0	50	74	65.0	15.0	14.0	6.0	79:21	64.6	42.9
3	A	20.0	25	15	69.0	15.0	12.0	4.0	81:19	70.4	57.9
4	A	20.0	50	75	65.5	14.5	14.5	5.5	80:20	63.8	45.0
5	A	22.0	25	18	71.5	14.5	10.5	3.5	82:18	74.4	61.1
6	A	22.0	50	80	66.0	16.0	13.0	5.0	79:21	67.1	52.4
7	B	14.5	50	40	61.5	16.0	15.5	7.0	77:23	59.1	39.1
8	B	20.0	25	11	74.0	13.0	10.0	3.0	84:16	76.2	62.5
9	B	20.0	50	71	66.0	14.5	14.0	5.5	80:20	65.0	45.0
10	B	22.0	50	73	67.5	14.0	13.5	5.0	81:19	66.7	47.4
11	C	14.5	50	58	55.0	18.0	18.0	9.0	73:27	50.7	33.3
12	C	20.0	25	20	64.0	16.0	14.0	6.0	78:22	64.1	45.5
13	C	20.0	50	79	59.5	16.5	16.5	7.5	76:24	56.6	37.5
14	C	22.0	25	21	68.5	13.5	13.5	4.5	82:18	67.1	50.0
15	C	22.0	50	86	64.0	15.0	15.0	6.0	79:21	62.0	42.9

† A, ethyl ether; B, toluene–benzene (7:3); C, methylene chloride.

atmospheric pressure, to be carried out in high yield; moreover, the effect of pressure on asymmetric induction was perceptible (Table 4).[144]

Analysis of Felkin's stereochemical model[83] of the reaction between diene **206** and (*R*)-**1** fully confirmed the results presented above[145] (Fig. 10).

In the course of high-pressure studies of the Diels–Alder reaction with furan derivatives[146] it was found that the reaction of 2,5-dimethylfuran (**220**) with butyl glyoxylate (**207a**) is inconsistant with a (4+2) cycloaddition pathway.[147] The reaction of **220** with **207a** under high-pressure conditions afforded only product **222** instead of the expected cycloadduct **221** (Scheme 49). The structure of **222** and preliminary mechanistic studies suggested that the high-pressure reaction of **220** with **207a** is an ene type reaction.[147]

The course of asymmetric induction in this new reaction was investigated using (*R*)-**1** as a chiral carbonyl compound.[148] The reaction of (*R*)-**1** with **220** under high-pressure conditions gave the expected product **223** as a mixture of diastereoisomers in a 4:1 ratio (Scheme 50). The protection of the hydroxyl group of **223** with benzyl bromide afforded separable diastereoisomeric benzyl ethers **224** and **225**.

The direction of asymmetric induction in the high-pressure reaction of (*R*)-**1** with **220** was studied by chemical correlation. The way adopted, which can equally serve as a method for the synthesis of 2-deoxypentitols, is represented in Scheme 51.

The sequence of reactions started from the major isomer, optically pure **224**. Furan ring opening in

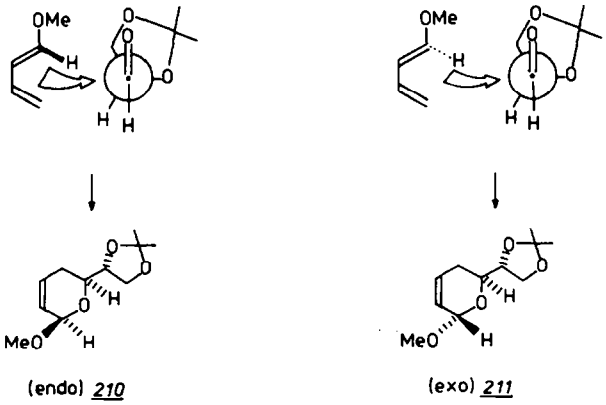
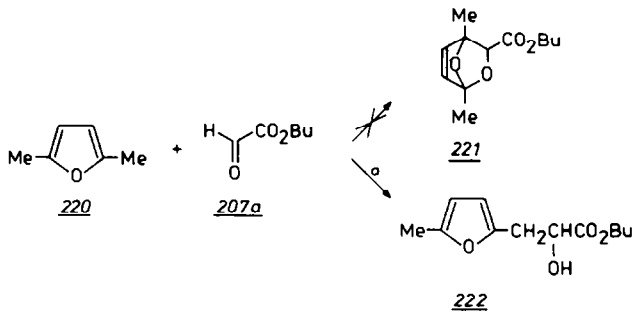
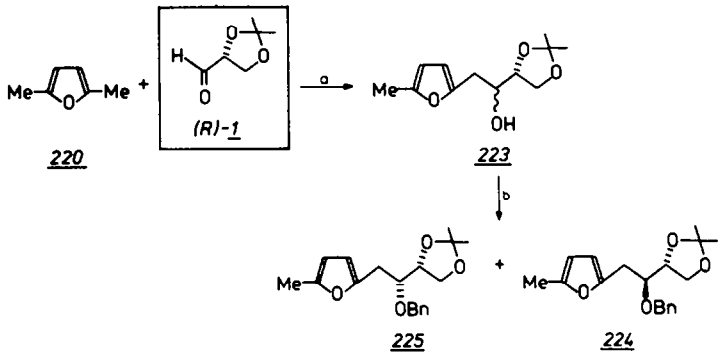


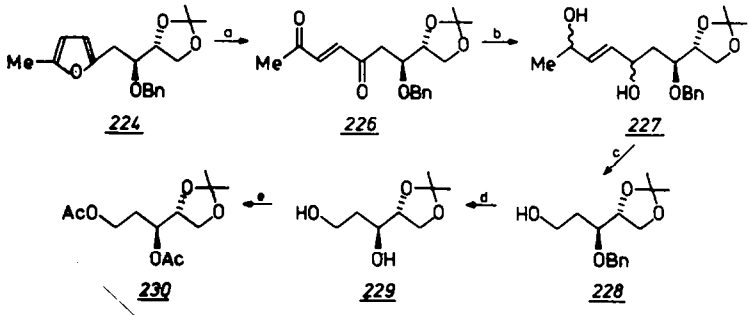
Fig. 10.



Scheme 49. Reactions: (a) CH_2Cl_2, 8 kbar, RT.



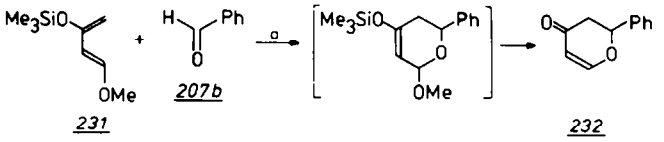
Scheme 50. Reagents: (a) CH_2Cl_2, 20 kbar, 55°; (b) $PhCH_2Br$, NaH, THF, DMF.



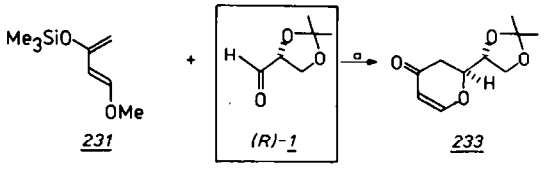
Scheme 51. Reagents: (a) PCC, AcONa, CH_2Cl_2; (b) DIBAL; (c) (i) OsO_4–$NaIO_4$, aq dioxane, (ii) $NaBH_4$; (d) H_2, Pd/C; (e) Ac_2O, pyridine.

order to give endione **226** was effected with pyridinium chlorochromate. DIBAL reduction gave diol **227** which was directly subjected to osmium tetroxide–sodium periodate reaction followed by sodium borohydride reduction. The 3-benzyloxy-4,5-O-isopropylidene derivative of 2-deoxy-D-ribitol (**228**) thus obtained was debenzylated by catalytic hydrogenation to give diol **229**. Acetylation of **229** afforded the 1,3-diacetoxy-4,5-O-isopropylidene derivative of 2-deoxy-D-ribitol (**230**) of known, absolute configuration and specific rotation.[148]

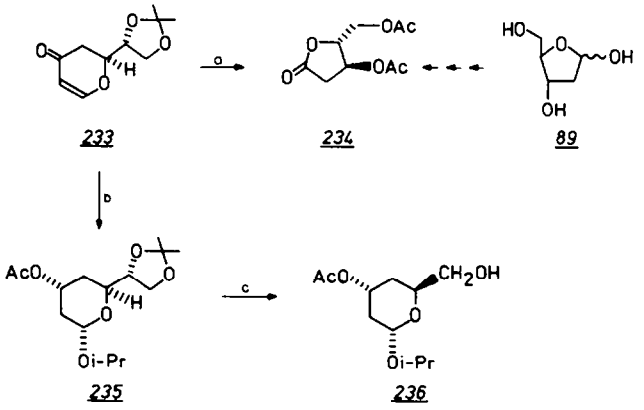
The reaction of highly "nucleophilic" derivatives of buta-1,3-diene, for example of (*E*)-1-methoxy-3-((trimethylsilyl)oxy)-buta-1,3-diene (**231**), with aldehydes were intensively studied by Danishefsky[149] (Scheme 52). He found that Lewis acids, e.g. zinc chloride or boron trifluoride, promote "cyclocondensation" with a broad spectum of aldehydes (e.g. **207b**) under mild conditions, affording dihydropyrones (e.g. **232**).[150] Moreover, application—as reaction catalysts—of rare-earth cations suitably complexed with solubilizing ligands (e.g. Eu(fod$_3$) permitted an efficient course of reaction under even milder conditions.[151]



Scheme 52. Reagents: (a) $ZnCl_2$, benzene.



Scheme 53. Reagents: (a) $ZnCl_2$, benzene.



Scheme 54. Reagents: (a) (i) O_3, (ii) H_2O_2, NaOH, (iii) Ac_2O, pyridine; (b) (i) i-PrOH, Me_2CO, 4 Å molecular sieves, (ii) L-selectride, THF, (iii) Ac_2O, pyridine; (c) (i) AcOH, H_2O, (ii) $NaIO_4$, (iii) $NaBH_4$.

The reaction of (*R*)-**1** with diene **231**, in the presence of anhydrous zinc chloride, afforded dihydropyrone derivative **233** in 72% yield[152] (Scheme 53). Likewise, an analogous reaction of (*S*)-**1** gave rise to enantiomer of **233**.

The 5*S* configuration of **233** follows from its correlation with 2-deoxyribonolactone (Scheme 54). This was accomplished by ozonolysis followed by oxidative fragmentation of the dihydropyrane ring. Acetylation of synthetic 2-deoxyribonolactone afforded **234** which was identical with the authentic material prepared from 2-deoxyribose (**89**). In Scheme 54 the convertibility of **233** to the optically pure 2,4-dideoxy-D-glucose derivative **236** is also demonstrated.[152]

Analysis of the classical Cram rule formulation indicates that (*R*)-**1** should give rise to (5*S*, 6*R*)-heptulose **233**. Alternatively, according to a chelation model wherein X^+ imposes a *syn* relationship between the formyl and two neighbouring oxygen functions, (5*R*, 6*R*)-heptulose would be expected[152] (Fig. 11).

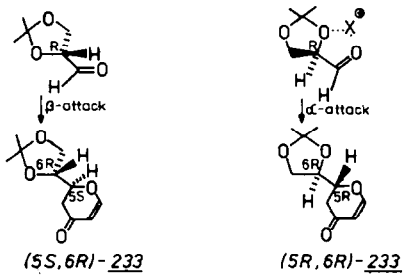
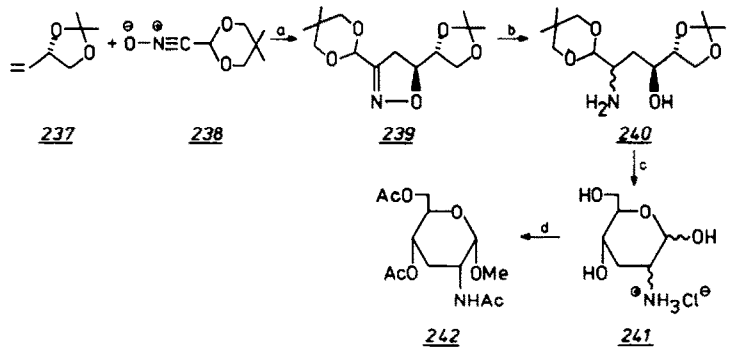


Fig. 11.



Scheme 55. Reagents: (a) PhNCO, Et_3N; (b) $LiAlH_4$; (c) 6 N HCl; (d) (i) Ac_2O, OH^-, (ii) MeOH, BF_3, (iii) Ac_2O, DMAP.

5.2. 1,3-*Dipolar cycloaddition*

Δ^2-Isoxazolines, prepared by the cycloaddition of a nitrile oxide to an alkane, are now widely used in synthesis.[153] There are two approaches to the preparation of chiral Δ^2-isoxazolines: (1) the addition of an achiral nitrile oxide to a chiral alkene, and (2) the addition of a chiral nitrile oxide to an achiral alkene. Nitrile oxides are usually generated *in situ* by dehydration of the corresponding nitro compound,[154] or by dehydrochlorination of a chloro-aldoxime.[155]

The first approach was used by Jäger and Schohe[156] in the synthesis of an amino sugar, D-lividosamine (**242**), as shown in Scheme 55.

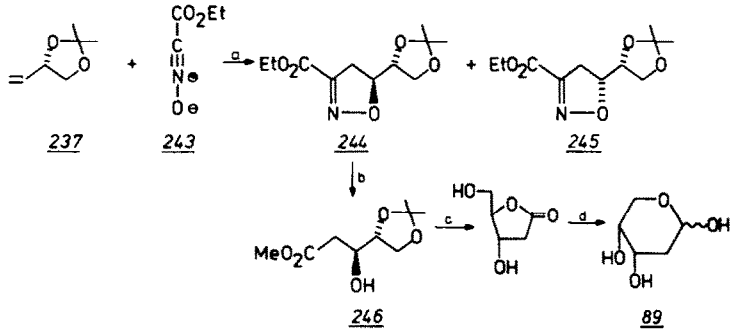
The cycloaddition of nitrile oxide **238**, generated *in situ* from the corresponding nitroacetaldehyde acetal, to chiral olefin **237**, prepared from (*R*)-2,3-O-isopropylideneglyceraldehyde (**1**) by the Wittig procedure,[157] afforded the *anti* isoxazoline **239** in 58% yield. Lithium aluminium hydride reduction proceeded with 4:1 selectivity to give **240**, which after hydrolysis furnished salt **241**. The latter was transformed in a three-step sequence into a derivative of D-lividosamine **242**.

The same chiral olefin **237**[157] was applied by Kozikowski and Ghosh in the synthesis of 2-deoxyribose (**89**)[158] (Scheme 56).

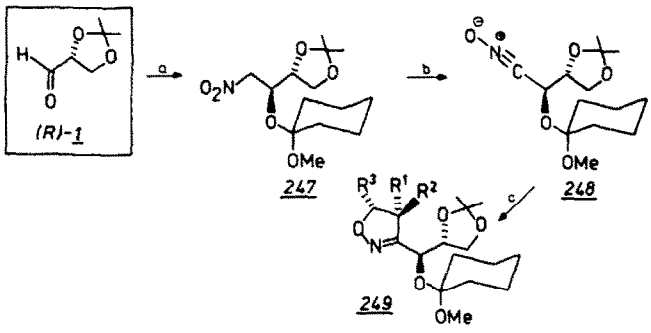
Olefin **237** was reacted with (carboethoxy)formonitrile oxide (**243**)[159] to afford an 8:2 mixture of diastereoisomeric cycloadducts **244** and **245**. The major isomer **244** was heated with sodium hydroxide, then acidified and finally treated with diazomethane, yielding **246**. Trifluoroacetic acid treatment followed by bis(3-methyl-2-butyl)borane reduction of intermediate lactone gave 2-deoxy-D-ribose (**89**).

The second approach was successfully utilized by Kozikowski *et al.*[160] (Scheme 57). Nitrile oxide **248** was generated *in situ* by treatment of **247** (obtained from (*R*)-**1**) with phenyl isocyanate and triethylamine and then trapped in good yield by an appropriate olefin.

Resulting isoxazoline **249** was applied in the synthesis of chiral β-hydroxyacids.[160] Similar investigations, using chiral nitrile oxide **248**, were also carried out by Jones *et al.*[161]



Scheme 56. Reagents: (a) Et_2O; (b) (i) 10% NaOH, EtOH, (ii) H^+, (iii) CH_2N_2; (c) CF_3CO_2H, H_2O; (d) thexylborane, THF.



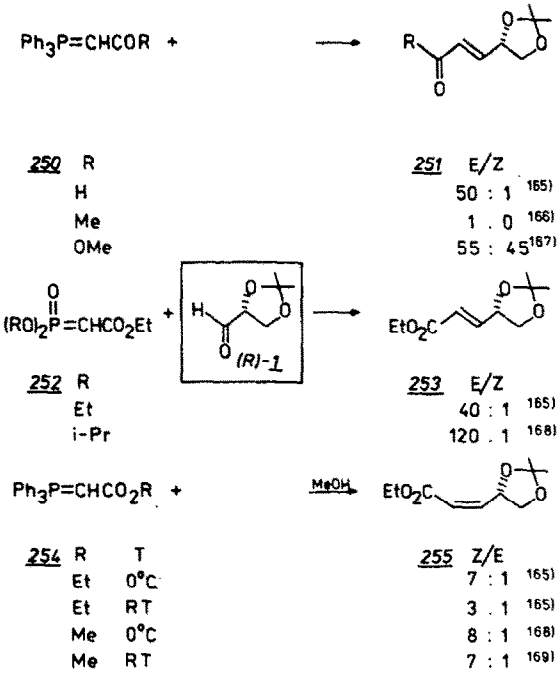
Scheme 57. Reagents: (a) (i) $MeNO_2$, KF, (ii) cyclohexan-1-ol methyl ether; (b) PhNCO, Et_3N; (c) $R^1R^2C{=}CHR^3$.

6. WITTIG TYPE REACTIONS

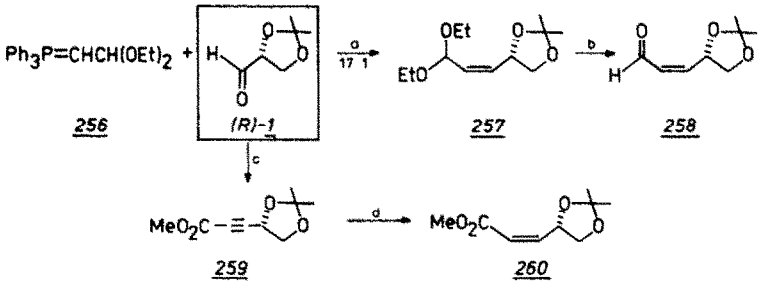
The carbonyl group of 2,3-O-diisopropylideneglyceraldehyde (1) not only participates in reactions leading to formation of a new chiral centre, but it also may be transformed into another functionality. This section gives a discussion on the Wittig reaction[162] permitting introduction of C=C bond to replace the formyl group of 1; the possibilities of stereoselective functionalization of this newly formed double bond are also presented.

The mechanism of the Wittig reaction remains still unclear and thus factors governing *Z*/*E* selectivity are not well known.[163] Nevertheless, some conclusions concerning the effect of the type of Wittig reagent and of the reaction conditions on *Z*/*E* selectivity were reached. Namely, it is known that application of stabilized organophosphorus compounds in non-polar solvents yields products with the *E*-configuration, whereas in alcohol-type solvents isomer *Z* predominates. In the case of a non-stabilized Wittig reagent, there is usually predominance of the *Z*-isomer.

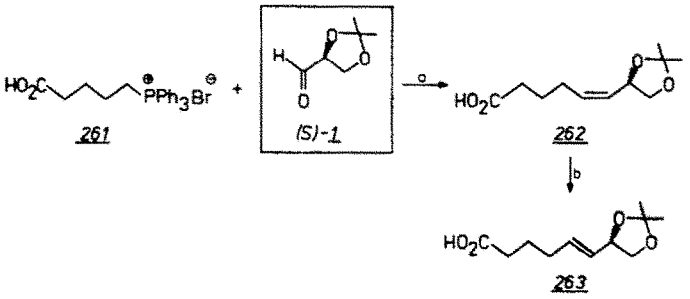
In 2,3-O-isopropylideneglyceraldehyde (1), the chiral centre of the dioxolane ring seems to play no part in the stereochemistry of the reaction. The *E*/*Z* ratio mainly depends on the nature of the ylide and on the reaction conditions. The first reaction of 1 with a stabilized Wittig reagent was reported in 1962,[164] without, however, determination of the *E*/*Z* ratio. Examples of reactions of 1 with various stabilized Wittig reagents, generally leading to predominance of isomer *E*, are presented in Scheme 58.



Scheme 58.



Scheme 59. Reagents: (a) THF; (b) 0.04 M *p*-TsOH, Me_2CO, H_2O; (c) (i) $PhHgCCl_2Br$, Ph_3P, (ii) BuLi, (iii) MeOCOCl; (d) H_2, $Pd/CaCO_3$.



Scheme 60. Reagents: (a) CH_2=S(O)Me; (b) $(PhS)_2$, *hv*.

The use of Bestmann reagent **250** (R = H)[170] afforded very high selectivity; product **251** (R = H) could also be obtained by other methods.[92,171] Using the Horner–Emmons modification of the Wittig reaction, virtually only isomer *E* is formed (Scheme 58). Excellent selectivity was obtained upon application of phosphonate ester with the isopropyl group **252** (R = i-Pr).[168,172] The reaction of stabilized Wittig reagents in methanol seems to be a very convenient method for preparation of *Z*-α,β-unsaturated esters,[165] though the selectivity is not very high (Scheme 58). The use of Bestmann reagent **256**[170] afforded much better selectivity (Scheme 59); reaction product **257** could be transformed into α,β-unsaturated aldehyde *Z*-**258** by acidic hydrolysis.[165]

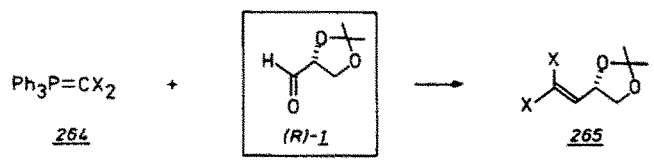
Stereospecific synthesis of *Z*-α,β-unsaturated ester **260** was also reported by Minami *et al.*[168] (Scheme 59).

In the reaction with non-stabilized Wittig reagents,[173–175] (*S*)-**1** yielded either exclusively or predominantly the *Z*-isomer. Scheme 60 presents the first and second step of the synthesis of leukotriene LTA_4 by Rokach *et al.*[174] (see Section 7), during which the selectively formed *Z*-double bond in **262** was photochemically isomerized to give compound *E*-**263**.

Wittig reagents of type **264**, applied in reactions with (*R*)-**1** afforded respective olefins **265**[157,176,177] (Scheme 61).

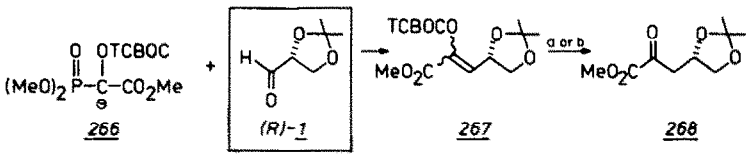
Anion **266** generated from the corresponding phosphonate by treatment with lithium or potassium hexamethyldisilazane, was reacted with (*R*)-**1** to give protected enol carbonate **267**. The latter was transformed into α-ketoester **268**[178] (Scheme 62).

α,β-Unsaturated phosphonates[179] and their fluorine derivatives[180] were also obtained using the Horner–Emmons modification. Wittig type reactions of 2,3-O-isopropylideneglyceraldehyde (**1**) for which no selectivity data are available will not be discussed in this report.[181–183]

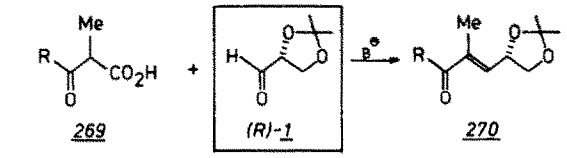


X = H,[157] Me,[176] Br[177]

Scheme 61.



Scheme 62. Reagents: (a) Zn, H_2O; (b) (i) Zn, TMSCl, THF, (ii) H^+.



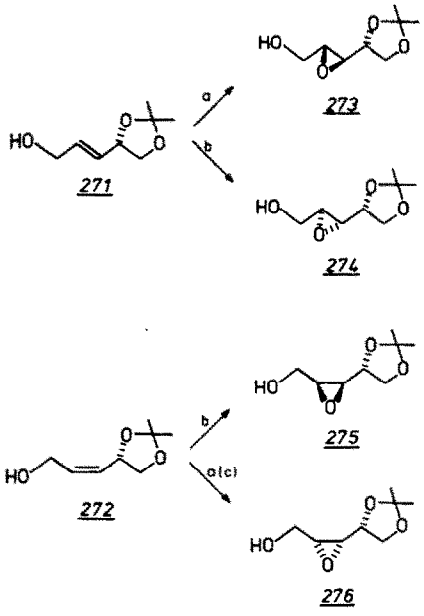
Scheme 63.

Certain compounds obtainable by Wittig reaction could also be prepared by the Knoevenagel–Doebner method[31,184] (Scheme 63).

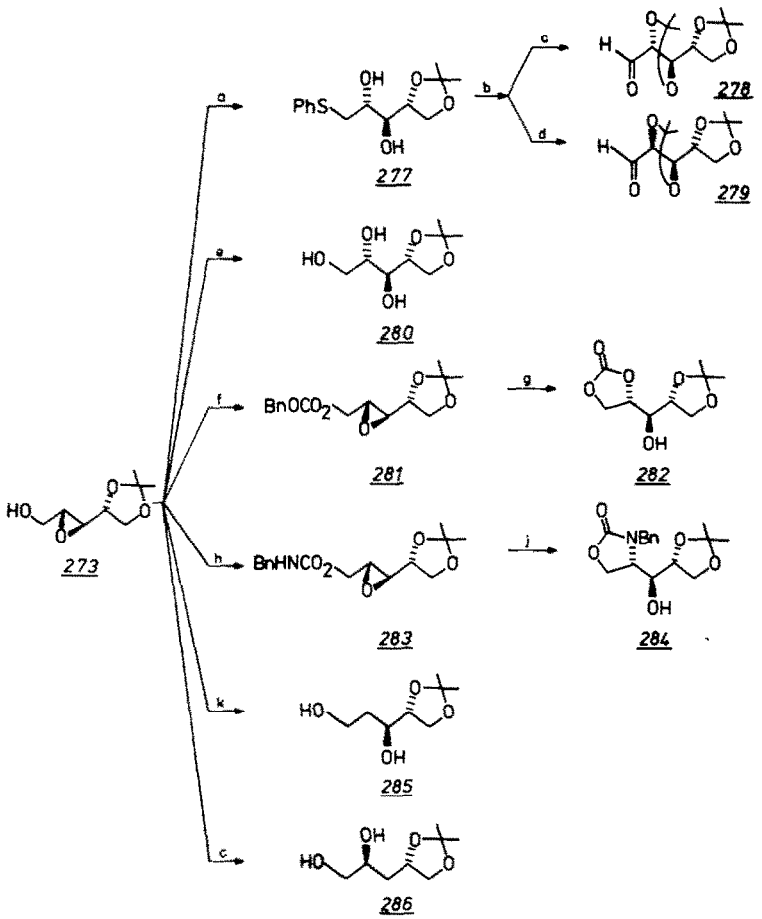
The products of Wittig reaction with (*R*)-1 were utilized by Kishi and co-workers[168,185] and by Sharpless and co-workers[165,186–188] for the synthesis of polyhydroxy open-chain chiral compounds. These authors investigated asymmetric epoxidation[189] of the allylic double bond in **271** and **272**, obtained from the respective α,β-unsaturated carbonyl compounds by reduction with DIBAL or sodium borohydride (Scheme 64).

There was very high selectivity in formation of epoxides **273** and **274** from *E*-olefin **271** (> 20 : 1) and of epoxide **275** from *Z*-olefin **272** (> 12 : 1); in the latter case, the reaction was very slow (55% yield after 2 weeks). Epoxidation of **272** with the use of (−)-diethyl tartrate also proceeded very slowly and furnished the diastereoisomeric mixture (**275** + **276**) in a 3 : 2 ratio. When *m*-chloroperbenzoic acid was applied in this epoxidation, the diastereoisomeric mixture (**275** + **276**) in a 1.0 : 1.1 ratio was formed.

Various transformations of epoxides **273**–**276** were carried out; they are presented in Scheme 65 being exemplified by **273** as starting material.



Scheme 64. Reagents: (a) $Ti(Oi\text{-}Pr)_4$, (−)DET, TBHP; (b) $Ti(Oi\text{-}Pr)_4$, (+)DET, TBHP; (c) *m*-CPBA.



Scheme 65. Reagents: (a) PhSH, NaOH; (b) (i) $Me_2C(OMe)_2$, H^+, (ii) *m*-CPBA, (iii) Ac_2O, AcONa; (c) DIBAL; (d) K_2CO_3, MeOH; (e) NaOH; (f) BnOCOCl, pyridine; (g) $AlCl_3$; (h) BnNCO, $(i\text{-}Pr)_2EtN$; (j) t-BuOK; (k) Red-Al.

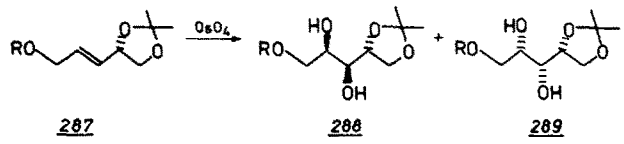
Payne rearrangement[190] stereospecifically afforded diol **277** which could be transformed either into D-ribose derivative **278** or—via epimerization of the centre in position α with respect to the carbonyl group—into D-arabinose derivative **279**. The reaction sequence transforming (*R*)-**1** into **278** and **279** or into either one of the two remaining diastereoisomeric pentoses represents a method for reiterative two-carbon chain extension to be used in the synthesis of sugars and related compounds.[165,187,188] Application of the hydroxyl ion in Payne rearrangement yielded triol **280** with high selectivity (15 : 1). Protected pentitol **282** and amino compound **284** could in turn be obtained by intramolecular opening by the epoxide ring, starting from carbonate **281** or urethane **283**. By reduction of epoxide **273**, 1,3-diol **285** and probably 1,2-diol **286** could be prepared selectively.[168]

Moreover, studies were made of *cis*-hydroxylation of the double bond in **287** and **290**, using stoichiometric (S) and catalytic (C) amounts of osmium tetraoxide.[191–193] The results shown in Scheme 66 indicate that selectivity varied from moderate to high. Olefin *Z*, as compared with olefin *E*, exhibited higher selectivity.

Other types of functionalization of the double bond formed by Wittig reaction are recorded in Scheme 67.

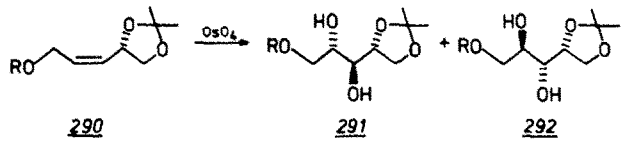
7. TOTAL SYNTHESIS OF NATURAL PRODUCTS

The present survey indicates that 2,3-O-isopropylideneglyceraldehyde (**1**) is a valuable, readily available chiral substrate susceptible to various transformations which may be useful for stereocontrolled syntheses. For example, optically active compound **1** can be applied in the syntheses of: (1) other simple chiral synthons (Section 2), (2) monosaccharides, their derivatives and other polyhydroxyl systems (Sections 3–5), and (3) natural products of a more complex structure. The first



287 288 289

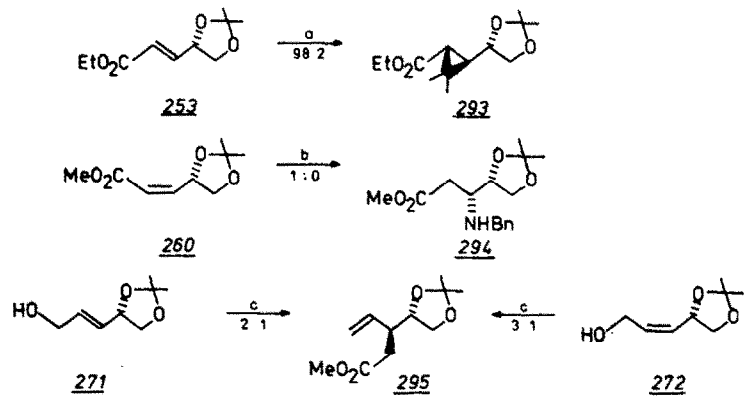
R		
H	S	3.3 : 1.0
	C	3.0 : 1.0
COMe	S	4.2 : 1.0
	C	4.0 : 1.0
$SiPh_2t$-Bu	S	3 3 : 1.0
	C	3.1 : 1.0



290 291 292

R		
H	S	6.3 : 1.0
	C	6.0 : 1 0
COMe	S	6.3 . 1.0
	C	6 1 . 1.0
$SiPh_2t$-Bu	S	8.0 : 1.0
	C	7.2 : 1.0

Scheme 66.

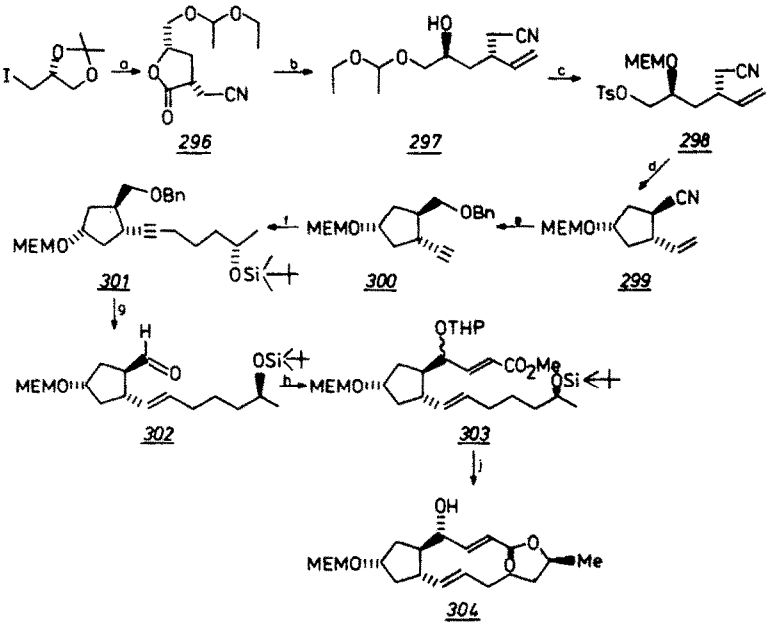


Scheme 67. Reagents: (a) $Ph_3P^+CHMe_2Br^-$;[183] (b) $BuNH_2$;[169] (c) $MeC(OMe)_3$, $EtCO_2H$.[167]

two instances usually involve relatively short, few-stage reaction sequences; most of these sequences were earlier mentioned. In the third case, longer reaction sequences are usually necessary. The centre of chirality of **1** is utilized for: (1) stereocontrolled generation of a new centre of chirality constituting part of the chiral moiety of the final molecule, and (2) its introduction into the final molecule. From among the total syntheses reported, examples illustrating both above-mentioned applications of **1** are described in this section.

(*R*)-2,3-O-Isopropylideneglyceraldehyde (**1**) was applied in the first synthesis of optically pure (+)-brefeldin A performed by Kitahara *et al.*[194] (Scheme 68).

Iodide **53** prepared from (*R*)-**1** was subjected to a sequence of reactions leading to lactone **296**. The new centre of chirality, formed at this stage was, however, generated with moderate selectivity (64 : 36). The major isomer **296** was converted into monoprotected diol **297**, and then into tosylate **298**, using typical reactions. The key step of the synthesis, i.e. cyclization, afforded a cyclopentane system, with marked predominance of isomer *trans*-**299** (92 : 8). Compound **299** was transformed into acetylene derivative **300** which in the reaction with an appropriate iodide yielded **301** containing all essential

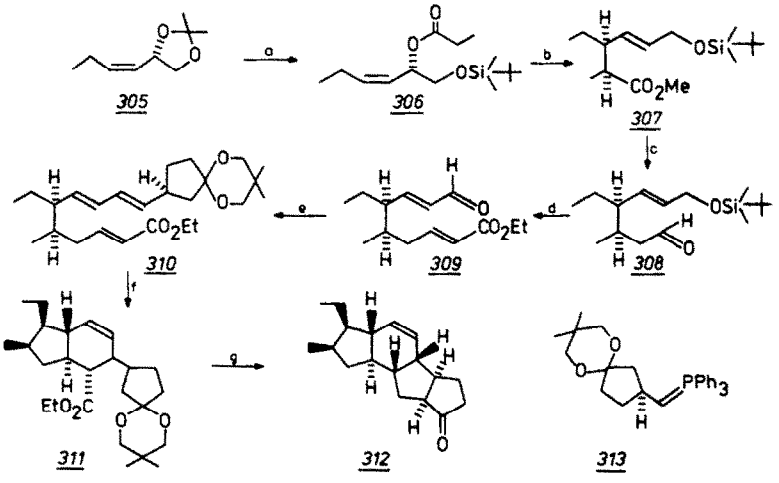


Scheme 68. Reagents: (a) (i) $NaCH(CO_2Et)_2$, (ii) NaOH, MeOH, H_2O, (iii) 2 N H_2SO_4, (iv) HCHO aq, Et_2NH, EtOH, (v) MeI, THF, (vi) NaCN, DMF, (vii) $EtOCH{=}CH_2$, PPTS; (b) (i) DIBAL, (ii) $Ph_3P{=}CH_2$, DME; (c) (i) MEMCl, (ii) AcOH, H_2O, (iii) TsCl, pyridine; (d) $NaN(TMS)_2$, benzene; (e) (i) NaOH, (ii) CH_2N_2, (iii) $LiAlH_4$, (iv) BuCl, NaH, (v) pyridine · HBr_3, $CHCl_3$, (vi) $NaNH_2$; (f) BuLi, $ICH_2(CH_2)_2CH(OSit\text{-}BuMe_2)Me$, HMPA, THF; (g) (i) Na, NH_3, (ii) PCC, AcONa; (h) (i) $O_2NCH_2CH_2CO_2Me$, $(i\text{-}Pr)_2NH$, DMSO, (ii) pyrrolidine, HMPA, (iii) 2H-pyran; (j) Corey's route.[195]

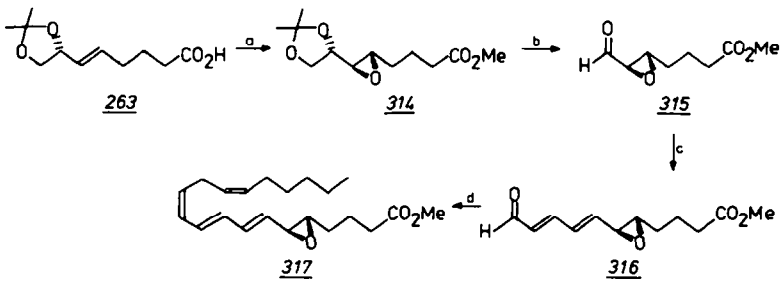
centres of chirality. Compound **303** was obtained as an epimeric mixture which via the previously reported pathway was converted into final compound **304**.

The synthesis of the tetracyclic fragment of ikarugomycin[175] is presented in Scheme 69.

Wittig reaction of (*R*)-**1** afforded virtually pure *Z*-olefin **305** which was then transformed into propionate **306**. Ireland reaction yielded ester **307** with good selectivity (84:16); after its chain extension by one carbon atom, it was converted into aldehyde **308** which by Horner–Emmons reaction selectively furnished *E*-α,β-unsaturated ester **309**. Compound **310** was obtained from **309** by Wittig reaction with reagent **313**, in the form of a mixture of *E,E*- and *E,Z*-isomers which was then isomerized using iodine to give the pure *E,E*-isomer. Thus a system of three double bonds with stereochemistry corresponding to intramolecular Diels–Alder cycloaddition was obtained. This reaction proceeding



Scheme 69. Reagents: (a) (i) 1 N HCl, (ii) TBDMSCl, Et_3N, DMAP, (iii) EtCOCl, pyridine; (b) (i) LDA, (ii) TMSCl, (iii) CH_2N_2; (c) (i) DIBAL, (ii) TsCl, pyridine, (iii) KCN, (iv) DIBAL, (v) AcONa, AcOH, H_2O; (d) (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, (ii) AcOH, H_2O, THF, (iii) PDC; (e) (i) **313**, (ii) I_2; (f) BHT; (g) (i) DIBAL, (ii) 0.5 N HCl, THF, (iii) TsCl, pyridine, (iv) t-BuOK.



Scheme 70. Reagents: (a) (i) CH_2N_2, (ii) *m*-CPBA, CH_2Cl_2; (b) $NaIO_4$, AcOH, H_2O; (c) $Ph_3P{=}CHCHO$, benzene; (d) $Ph_3P^+(CH_2)_2CH{=}CH(CH_2)_4Me$.

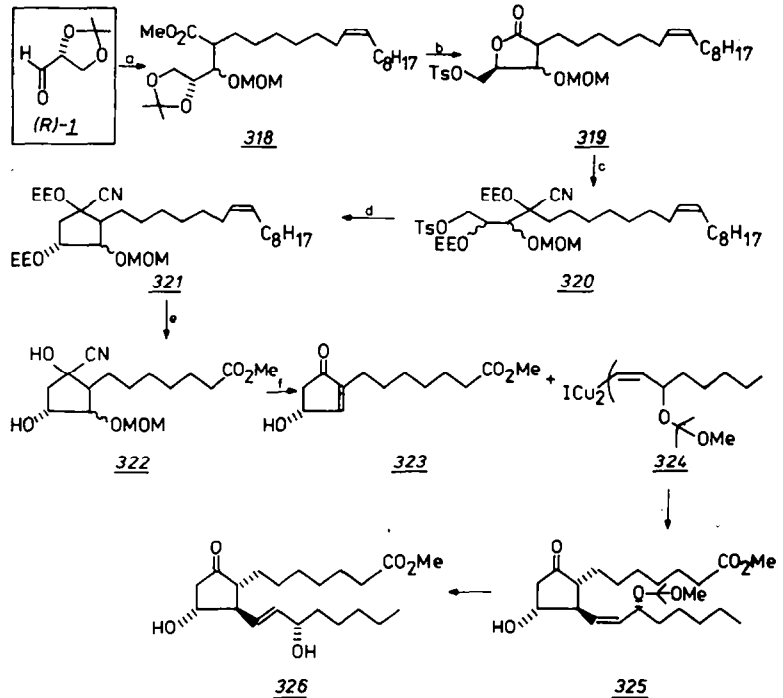
with formation of four new centres of chirality afforded **311** with high selectivity (5 : 1). Final compound **312** was then prepared using a four-step reaction sequence.

Rokach *et al.*[174] reported a synthesis of Leukotriene LTA_4, starting from (*S*)-**1** (Scheme 70).

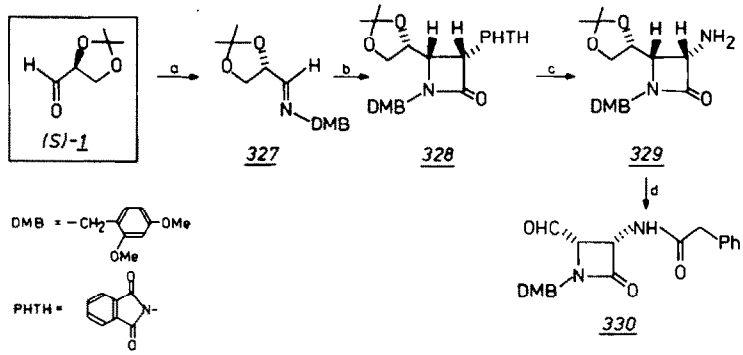
Preparation of unsaturated acid **263** was described in Section 6 (Scheme 60). Epoxidation of the *E*-double bond in **263**, using *m*-chloroperbenzoic acid led to product **314** with fairly low selectivity (2 : 1). However, diastereoisomeric epoxides could be resolved using conventional chromatographic techniques. Hydrolysis with simultaneous diol cleavage afforded aldehyde **315** which subjected to Wittig reaction sequences gave final product **317**.

Stork and Takahashi[196] published the synthesis of prostaglandin PGE_1, starting from (*R*)-**1** (Scheme 71).

Condensation of (*R*)-**1** with an anion generated from methyl oleate yielded a diastereoisomeric mixture whose composition was not analyzed, because both chirality centres created in this step were destroyed in the subsequent reactions. After protection of the hydroxyl group of the condensation product, **318** was obtained and transformed into lactone **319** in two steps. Subsequently protected cyanohydrine **320** was obtained and then cyclized; product **321** was converted into cyclopentenone **323** via deprotection of the hydroxyl groups, oxidation of side-chain and elimination reaction. Compound



Scheme 71. Reagents: (a) (i) $H_{17}C_8CH{=}CHC_7H_{14}CO_2Me$, LDA, THF, HMPA, (ii) MOMCl, $(i\text{-}Pr)_2NH$; (b) (i) H_2SO_4, THF, (iii) TsCl, pyridine; (c) (i) DIBAL, (ii) HCN, EtOH, NH_3, (iii) $EtOCH{=}CH_2$, $HCl_{conc.}$; (d) hexamethyldisilazane, benzene; (e) (i) $NaIO_4$, $KMnO_4$, (ii) H^+, H_2O, (iii) CH_2N_2; (f) (i) 2% NaOH, ethyl ether, THF, (ii) 0.1 N HCl.



Scheme 72. Reagents: (a) $DMBNH_2$; (b) $PHTH–CH_2COCl$, Et_3N, CH_2Cl_2; (c) NH_2NHMe, CH_2Cl_2; (d) (i) $PhCH_2OCOCl$, butylene oxide, (ii) TsOH, THF, H_2O, (iii) $NaIO_4$, MeOH.

323 was then reacted with racemic cuprate **324** to give—as a result of kinetic competition—only one diastereoisomer **325** which was transformed into PGE_1(**326**).

Optically pure β-lactam systems could be prepared by a few methods using (*R*)-**1** as starting material.[130,167,197] One of them,[197] shown in Scheme 72, involved the reaction of imine **327** with the acid chloride derivative of phthalimide, and it enables direct closing of the β-lactam ring; product **328** was converted into amine **329**, and then into aldehyde **330**.

A few further examples illustrate the use of 2,3-O-isopropylideneglyceraldehyde (**1**) for preparation of compounds with only one centre of chirality, with the same configuration as that of the starting aldehyde. Corey and Kang's[171] synthesis of 11-(*R*)-HETE is presented in Scheme 73.

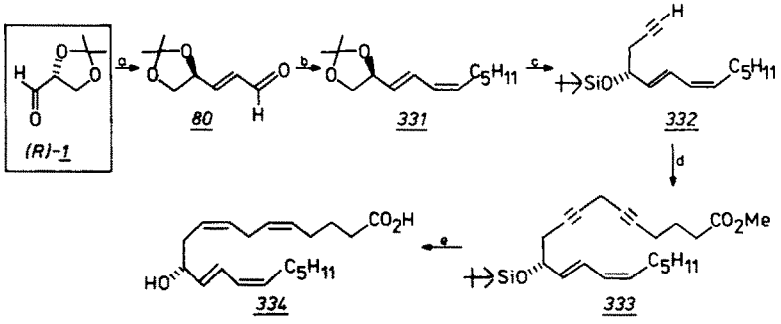
α,β-Unsaturated aldehyde **80** was synthesized from (*R*)-**1** via an acetylenic intermediate, and it was subjected to a Wittig reaction to yield *E,Z*-diene **331**; the latter after epoxide formation and selective ring opening in the terminal position furnished **332**. This product was reacted with an appropriate allene bromide to give 1,4-diyne unit **333**; triple bonds were hydrogenated to *Z,Z*-1,4-diene in the presence of Lindlar catalyst. Two subsequent standard reactions afforded final tetraene **334**.

Scheme 74 shows the synthesis of a well-known pheromone, ipsdienol.[176,198]

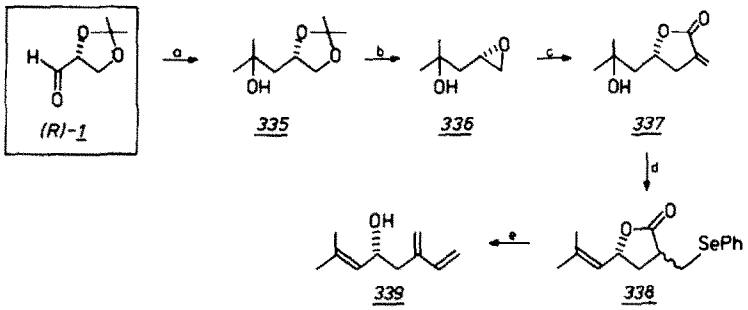
Alcohol **335** was obtained from (*R*)-**1** by Wittig reaction followed by a mercuration–reduction procedure. Compound **335** was transformed into epoxide **336** by a typical reaction sequence. Opening of the oxirane ring upon use of an anion generated from ethyl malonate, followed by reaction with formaldehyde, furnished lactone **337**. The methylene group was protected by Michael addition of selenophenol; subsequent dehydration gave **338** which in two steps was finally transformed into **339**.

The synthesis of (*S*)-(−)-tulipaline **B**[199] is illustrated in Scheme 75.

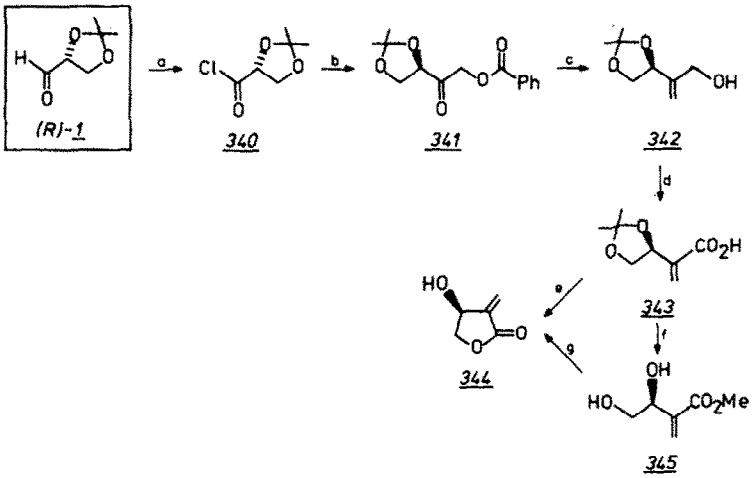
Acid chloride **340** was obtained from (*R*)-**1** as a result of potassium permanganate oxidation under alkaline conditions, followed by treatment with oxalyl chloride. Compound **340** was then transformed into benzoate **341**. Using typical reactions, acid **343** and final compound **344** were obtained. Moreover, known dihydroxyester **345** was prepared by esterification using methyl iodide and sodium hydride.



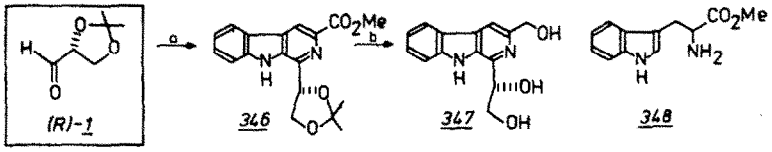
Scheme 73. Reagents: (a) (i) EtOC≡CLi, THF, (ii) H_2, Lindlar catalyst, Et_3N, (iii) MesOH, CH_2Cl_2; (b) $Ph_3P^+CH_2C_5H_{11}I^-$, CH_2=SOMe, DMSO; (c) (i) 0.005 N HCl, MeCN, H_2O, (ii) TsCl, pyridine, (iii) DBU, THF, (iv) $CH{\equiv}CLi{\cdot}(CH_2NH_2)_2$, HMPA, THF, (v) Me_2(t-Bu)SiCl, imidazole, DMF; (d) (i) BuLi, (ii) $Cu_2(CN)_2$, (iii) CH_2=C=C(Br)$C_3H_6CO_2Me$, THF, HMPA; (e) (i) H_2, Lindlar catalyst, Et_3N, (ii) Bu_4NF, THF, (iii) NaOH.



Scheme 74. Reagents: (a) (i) i-PrP$^+$Ph$_3$I$^-$, $^-$CH$_2$SOMe, DMSO, (ii) Hg(OAc)$_2$, THF, H$_2$O, (iii) NaBH$_4$, NaOH, H$_2$O; (b) (i) HCl, EtOH, (ii) TsCl, pyridine, (iii) KOH, H$_2$O; (c) (i) CH$_2$(CO$_2$Et)$_2$, EtONa, (ii) HCHO, Et$_2$NH; (d) (i) PhSeH, EtOH, (ii) POCl$_3$, pyridine, (e) (i) DIBAL, THF, (ii) Ph$_3$P$^+$MeBr$^-$, $^-$CH$_2$SOMe, DMSO, THF.



Scheme 75. Reagents: (a) (i) KMnO$_4$, KOH, H$_2$O, (ii) (COCl)$_2$, pyridine, ethyl ether; (b) (i) CH$_2$N$_2$, ethyl ether, (ii) PhCO$_2$H, Cu, dioxane; (c) (i) Ph$_3$P$^+$MeI$^-$, THF, (ii) OH$^-$, H$_2$O; (d) (i) MnO$_2$, CH$_2$Cl, (ii) Ag$_2$O, CH$_2$Cl$_2$, H$_2$O; (e) 1 N HCl; (f) (i) NaH, MeI, HMPA, (ii) AcOH, H$_2$O; (g) NaOH, H$_2$O.



Scheme 76. Reagents: (a) (i) **348**, benzene, (ii) DDQ; (b) (i) LiBH$_4$, THF, (ii) AcOH, H$_2$O.

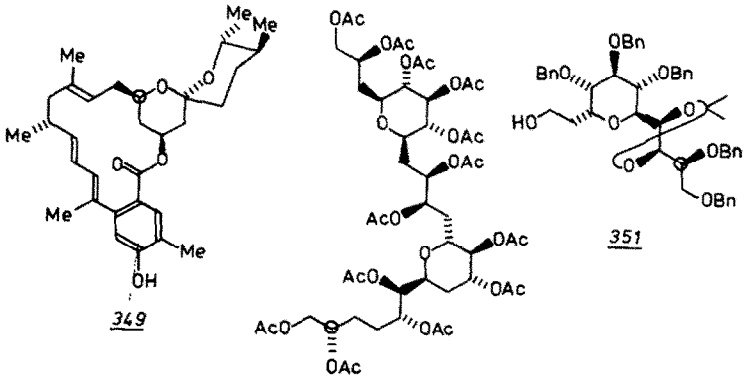


Fig. 12.

The synthesis of optically active forms of β-blockers involve utilization of 2,3-O-isopropylideneglyceraldehyde (1) as chirality source (Section 2); it is exemplified by the synthesis of pyridindolol[200] presented in Scheme 76.

Two examples shown in Fig. 12 illustrate the application of (*R*)-1 for the synthesis of other complex natural compounds, namely of milbemycin β_3 (**349**)[201] and of fragments of palytoxin **350** and **351**.[202] In Fig. 12, only three carbon units with a chirality centre originating from (*R*)-1 are shown schematically.

8. MISCELLANEOUS

Apart from the many examples of the applications of (*R*)- and (*S*)-2,3-O-isopropylideneglyceraldehyde (1) in stereocontrolled organic syntheses which are shown in this report, the title compound was also used in other chemical transformations. Thus biologically active compounds like massoilactone,[203] phosphorus-[204] and nitrogen-containing[205] carbohydrates as well as deoxysugars[206] were obtained starting from 1. Syntheses of phospholipids[207] and glycerol derivatives—both isotopically labelled[208] and unlabelled[209]—were carried out utilizing 1 as the chiral substrate. It also serves as a starting material in preparations of simple chiral compounds such as 2-(*S*)-benzyloxirane,[210] (*S*)-1,2-heptanediol,[211] cyclopentane system,[212] various C_5-building blocks,[213] β-ketoesters and pyrimidine derivatives,[214] vinyl phosphonates[215] and cyanohydrine derivative.[216] Reaction of 1 with aniline was also investigated.[217]

9. CONCLUSIONS

As can be seen from literature data presented above, aldehyde 1 is a versatile chiron, widely recognized, cheap and easily accessible from natural sources. However, the degree of stereoselectivity obtained in some reactions shown is not high enough to meet present demand, thus more work has to be done to understand all factors responsible for asymmetric induction. Higher stereoselectivities will surely expand the utility of this valuable chiral synthon. Finally, we feel that the near future will bring even more examples of synthetic sequences starting from the (*R*)- and (*S*)-2,3-O-isopropylideneglyceraldehyde.

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